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YOUR BIONIC FUTURE

Quarterly

Volume 10, Number 3

SCIENTIFIC AMERICAN PRESENTS

YOUR BIONIC FUTURE

How technology will change the way you live in the next millennium

Fall 1999 Vol. 10, No. 3

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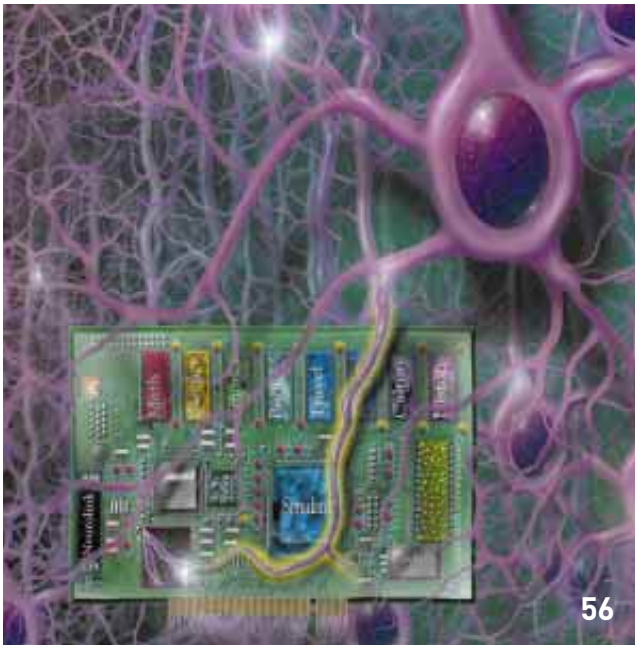

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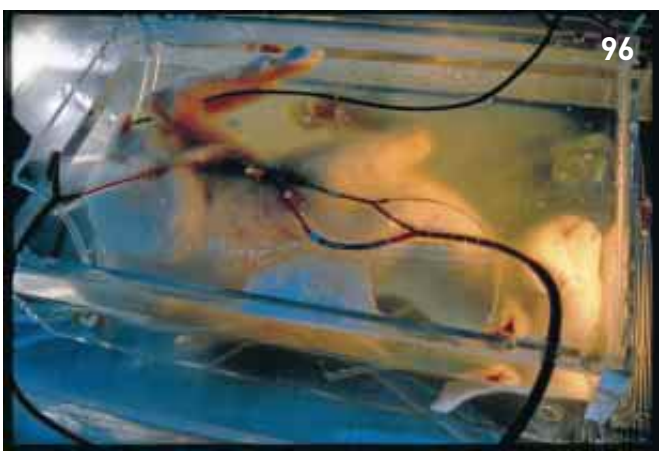

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SCIENTIFIC AMERICAN® PRESENTS

Your Bionic Future: How Technology Will Change the Way You Live in the Next Millennium is published by the staff of SCIENTIFIC AMERICAN, with project management by:

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YOUR BIONIC FUTURE

As life and technology merge, they will both become more interesting.

By Glenn Zorpette and Carol Ezzell, *issue editors*

TELEVISION AND SLOT MACHINES notwithstanding, the point of technology is to extend what we can do with our bodies, our senses and, most of all, our minds. In the century now closing, we have gone from gaping at electric lightbulbs and telephones to channel-surfing past images of a sunrise on Mars, to outbursts of pique if our e-mail takes more than a few minutes to get to the other side of the world.

And in the next decade or two, the revolution is finally going to get really interesting. Several of the most important but disparate scientific and engineering achievements of the 20th century—the blossoming of electronics, the discovery of DNA and the elucidation of human genetics—will be the basis for leaps in technology that will extend, enhance or augment human capabilities far more directly, personally and powerfully than ever before.

The heady assortment of biotechnologies, implants, wearables, artificial environments, synthetic sensations, and even demographic and societal shifts defies any attempt at concise categorization. But as our title boldly proclaims, we couldn't resist resurrecting the word "bionics," lately in a state of anachronistic limbo alongside the 1970s television adventures that made it a household word. Bionics often refers to the replacement of living parts with cybernetic ones, but more broadly it also means engineering better artificial systems through biological principles. That merger of the biological with the microelectronic is at the heart of most of the coming advances.

As scientists and engineers unleash fully the power of the gene and of the electron, they will transform bits and pieces of the most fundamental facets of our lives, including eating and reproducing, staying healthy, being entertained and recovering from serious illness. Big changes could even be in store for what we wear, how we attract mates and how we stave off the debilitating effects of getting older. Within a decade, we will see:

- A cloned human being. It is possible, in fact, that experiments are already under way in secret.
- An artificial womb for women who can't become—or don't want to be—pregnant.
- Replacement hearts and livers, custom-grown from the recipient's own versatile stem cells.
- Virtual reality that becomes far more vivid and compelling by adding the senses of smell and touch to those of sight and sound.
- Custom clothing, assembled automatically from highly detailed scans of the purchaser's body and sold at a cost not much higher than off-the-rack.
- Foods that counteract various ailments, such as noninsulin-dependent diabetes, cholera, high cholesterol or hepatitis B.
- A genetic vaccine that endows the user with bigger, harder muscles, without any need to break a sweat at the gym.

With only a few exceptions, the articles collected here extrapolate conservatively into the near future. Essentially all the predicted developments will follow directly from technologies or advances that have already been achieved in the laboratory. Take that genetic muscle vaccine: as this issue goes to press, a University of Pennsylvania researcher is exercising buff laboratory mice whose unnaturally muscular hind legs were created by injection. He has little doubt about the suitability of the treatment for humans.

The three exceptions to the mostly restrained tone of this issue are the articles by neurosurgeon Robert J. White, geneticist Dean Hamer and engineer-entrepreneur Ray Kurzweil, all of whom stake

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The **merging** of **biology and microelectronics** is at the heart of most of the **coming advances.**

out positions that are controversial among their peers. White raises the possibility of making the Frankenstein myth a reality as he declares that medical science is now capable of transplanting a human head onto a different body. Hamer uses today's scientific fact and his best guesses about tomorrow's technology to sketch a fictional account of a couple in the year 2250 customizing the genes that will underlie their baby's behavior and personality. Kurzweil argues not only that machines will eventually have human thoughts, emotions and consciousness but that their ability to share knowledge instantaneously will inexorably push them far past us in every category of endeavor, mental and otherwise.

Regardless of whether we ever see Frankenstein's monster, much less conscious machines, we already have enough details of the more immediate bionic future to let us raise some of the deeper questions about what it means. Depending on your viewpoint, there are plenty of uncomfortable if not alarming possible outcomes. Athletic competition, for example, could devolve into baroque spectacles that decide, basically, whose genetic enhancements (and work ethic) are best. Of course, it would be difficult to argue that such games would be intrinsically less interesting than today's contests, which pretty much decide whose natural genes (and work ethic) are best.

Since the 1970s such possibilities have tended to inspire relatively dark cultural movements. Examples include an entire subgenre of dystopian science fiction and one mad bomber. Historians and philosophers, too, are more likely now to analyze the negative ramifications of technology or even to attribute the endeavor to odd or unwholesome urges. Perhaps no one has written more entertainingly on the subject than the scholar William Irwin Thompson. In his 1991 book *The American Replacement of Nature*, he wrote:

> In truth, America is extremely uncomfortable with nature; hence its culturally sophisticated preference for the fake and nonnatural, from Cheez Whiz sprayed out of an aerosol can onto a Styrofoam potatoed chip, to Cool Whip smoothing out the absence of taste in those attractively red, genetically engineered monster strawberries. Any peasant with a dumb cow can make whipped cream, but it takes a chemical factory to make Cool Whip. It is the technological process and not the natural product that is important, and if it tastes bad, well, that's beside the point, for what that point is aimed at, is the escape from nature.

In the next decade or two the flight from nature will soar to new heights. The bright side of this transformation is potentially dazzling enough to drown out some of the dark visions. That is always the hope, of course. But the case now is unusually strong even if we base it on nothing more than the likelihood of powerful, sophisticated treatments for a host of dread genetic diseases and the frailties of old age. Those willing to grasp the implications of the coming fusion of biology and technology, with all its potential for beneficence and havoc, will find the exercise exhilarating.

ZACH GOLD (*woman*); KOB *StockFood (strawberry)*

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COUTURE CURES: THIS DRUG'S FOR YOU

Doctors may one day sneak a peek at your genes to determine which drugs will cure you and which might kill you. **By Karen Hopkin**

"ONE PILL makes you larger and one pill makes you small. And the ones that Mother gives you don't do anything at all."

Some things were so simple in the '60s. If Grace Slick were to sing of today's pharmacology, her verse would probably sound more like the fine print at the bottom of a glossy drug ad: This pill may make you larger or smaller. It may also cause headaches, vomiting, night blindness, impotence and heart failure.

Of course, pharmaceutical companies want to avoid litigation when they market their medications to the public. But the long list of possible effects—and side effects—that accompanies every drug on the market today also reflects the recognition that individuals differ in the way they respond to medications. And that response depends, in large part, on a person's genes.

Now scientists are beginning to take advantage of new techniques that allow them to collect and compare large volumes of information about gene sequences—and about drug action—to predict how a person will respond to a given drug. These techniques stand to speed up the way drugs are designed and tested and may even change the way doctors diagnose and treat disease in the future.

Researchers have long known that genetic alterations can lead to disease. Mutations in one gene cause cystic fibrosis; in another gene, sickle cell anemia. But it is now becoming clear that genetic differences can also affect how well a person absorbs, breaks down and responds to various drugs. The cholesterol-lowering drug pravastatin, for example, does nothing for people with high cholesterol who have a common variant of an enzyme called cholesteryl transfer protein.

Genetic variations can also render drugs toxic to certain individuals. Isoniazid, a tuberculosis drug, causes tingling, pain and weakness in the limbs of those who are termed slow acetylators. These individuals possess a less active form of the enzyme *N*-acetyltransferase, which normally helps to clear the drug from the body. Thus, the drug can outlive its usefulness and may stick around long enough to get in the way of other, normal biochemical processes. If slow acetylators receive procainamide, a drug commonly given after a heart attack, they stand a good chance of developing an autoimmune disease resembling lupus.

BALM OR BANE?

Enter pharmacogenomics, a new science that aims to use a systematic genome-wide analysis of genetic variation to see which drugs might work for you and which might make you sicker. The clues come in the form of single nucleotide polymorphisms, or SNPs (pronounced "snips")—genetic hot spots scattered along our chromosomes that can vary in DNA sequence from person to person. Researchers are now compiling an extensive catalogue of these SNPs in the hopes that they will be able to link particular genetic fingerprints with differences in drug response.

SNP testing would work something like this: a doctor or technician would extract DNA from a small sample of a person's blood or other body cells. The DNA would then be washed over a SNP chip—a glass slide studded with DNA fragments that represent all the common genetic variations in, say, a gene known to control how well a drug is absorbed. (Some SNPs correlate with good absorption and some with poor absorption.) The DNA from the

TOM MOORE

Drug vending machines that dole out designer doses on demand probably won't be popping up on street corners anytime soon. But scientists envision a day when physicians will prescribe pharmaceuticals tailored to our own specific genetic information, which we might carry around encoded on a credit-card-size plastic plate.

A physician could **biopsy a tumor**, grow the harvested cells on a chip and then test to see **which chemicals** would be most effective at **killing the cells.**

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patient would stick to whichever SNP it matched, and a scanner could then look at the chip and determine whether the person would be able to absorb the drug in question.

But beyond improving diagnostics, drug companies hope that pharmacogenomics will help them get more novel drugs to market. Currently 80 percent of drugs are shot down in early clinical trials because they are not effective or are even toxic, according to the Tufts Center for the Study of Drug Development at Tufts University. Pharmaceutical companies would like to boost the success rate of drug approval by testing new drugs only in individuals who are likely to show benefits from them during the clinical trial.

The problem is that people who are deemed genetically unresponsive might then fall through the cracks, observes William A. Haseltine, CEO of Human Genome Sciences in Rockville, Md. As it stands, pharmacogenomics is headed toward splintering the drug market, generating three or four different drugs that each might treat only tens of thousands of individuals with a particular disease—a scenario Haseltine views as "utter folly." Instead he favors using pharmacogenomics to develop new drugs aimed at treating the majority of people.

Using pharmacogenomics to select people who will respond to new drugs, Haseltine notes, "is a route around, not through, a major problem"—the problem being that it is difficult to develop drugs that work. Indeed, many companies are pursuing different methods for stepping up the flow through the pharmaceutical development pipeline. The goal, simply put, is to be able to generate and test the largest number of compounds in the shortest amount of time with the least amount of human effort. So researchers are turning to robots that can simultaneously analyze tiny volumes of thousands of samples—a process dubbed high-throughput screening. Then they use computers to process and keep track of all the results—and, in some cases, to suggest which drugs should be tested.

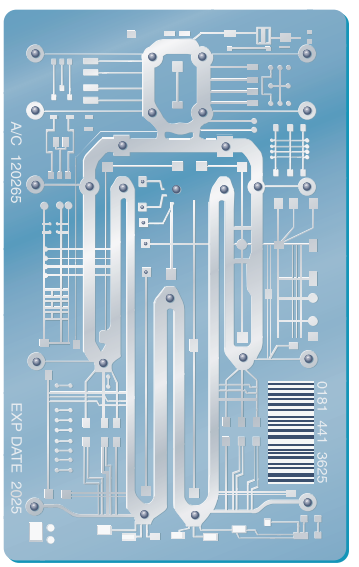
THE PHYSICAL OF THE FUTURE

"I SEE THIS is your first visit," says the doctor, looking up from her notes. "What seems to be the problem?" With a shuddering sigh, you describe your lack of energy, inability to sleep, disinterest in activities you once found pleasurable, and the crying—every day you cry. "Have you ever been treated for depression?" she asks, reaching for what looks like a small plastic tongue depressor. "Uh-uh," you gurgle, mouth agape, as the doctor scrapes a swath of cells from inside your cheek. "Then we'll just do a quick 'snip check,' and you can pick up your prescription this afternoon," she says, dropping the spatula into a vial and sending it off to the laboratory. There technicians will extract and analyze your DNA to determine which of the 837 antidepressants on the market will best chase away your blues.

Will pharmacogenomics usher in such an era of personalized medicine, in which our genetic fingerprints will determine the kind of medical treatment we receive? Will every trip to the clinic involve surrendering some DNA for sequencing? And once our DNA sequences can be easily accessed from a global database, will physicals be replaced by phone-ins?

Well, yes and no. First, it is important to keep in mind that genes aren't everything. "Many factors determine drug response," cautions William A. Haseltine of Human Genome Sciences. Genes are important, but so are the age, sex and general health of the patient, as well as the other drugs he or she might be taking. Still, scientists anticipate that genetic profiling may soon help doctors diagnose diseases and allow them to prescribe medications that will work best for an individual patient. "Most drugs only work on 30 or 40 percent of people," says Daniel Cohen of Genset in Paris. "Only aspirin works on almost everyone."

Genetic testing should help match the right drug at the right dose to the right patient without a lot of time-consuming trial and error. If you were clinically depressed, for example, a quick look at the results of a test called a P450 profile might indicate that you break down drugs so rapidly that you would probably clear certain antidepressants from your bloodstream before they could take effect. Or you might break them down so slowly that normal doses would make you antsy.



IAN WORPOLE

In addition to helping determine drug dosage and minimizing unwanted side effects, genetic screening may soon be used to predict a patient's predispositions to disease. Perhaps when you're 18 years old, you'll automatically be screened for your susceptibility to heart disease, diabetes, Alzheimer's disease, cancer and scores of other disorders. Armed with this knowledge, you might then be able to change the way you live or the foods you eat to boost the odds that you'll stay healthy.

Will we all eventually carry plastic plates the size of credit cards that are digitally encoded with all the genetic secrets stored in our genomes? "No, they'll probably be on chips implanted under our arms," jokes John Tallman, Neurogen's executive vice president. Although both options may someday be technologically possible, they will probably be a ways off. For one, investigators have yet to sequence one complete human genome. So rather than sequencing every one of the six billion nucleotide letters that make up your personal genetic code, for now pharmacogeneticists will very likely focus on the few hundred gene mutations, or SNPs, that have been shown to correlate with drug responsiveness or disease risk, says Francis S. Collins of the National Human Genome Research Institute. Ultimately, researchers hope such tests will cost a few dollars and yield results in an hour.

Genetic testing, of course, raises privacy issues. Will your employer or insurer be able to access your genetic profile? What about telemarketers? With any luck, legislators will pass laws designed to protect your genetic privacy long before the technology makes this future possible. Still, imagine answering the phone during dinner to hear a chirpy electronic voice dispense unwanted medical advice: "Isn't it time you started taking Progenitol?" —*K.H.*

Forget insurance cards. In the future your doctor might be more interested in your SNP chip, which will contain information about your single nucleotide polymorphisms (SNPs). These genetic sequences show how you differ from someone else in traits such as how fast your body is able to break down various drugs.

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Researchers at Neurogen, a pharmaceutical company in Branford, Conn., for example, use high-throughput computer modeling methods to select the most promising drugs from a "virtual library," a computer database that contains the molecular structures of billions and billions of chemical compounds not yet made. Say they want to develop a more effective antianxiety medication. The scientists browse through a few hundred million molecules in their virtual library and select a few dozen groups of compounds that might interact with the particular types of satellite-dish-like proteins called receptors on the surfaces of nerve cells in the brain that are specifically associated with anxiety. Drugs that bind to these receptors could prevent panic attacks by interfering with the chemistry that makes some people unnecessarily anxious. The compounds could then be synthesized and tested, and the results could be used to home in on the most promising antianxiety drugs. Combining such rational drug design with powerful computing tools allows investigators to test thousands of compounds in a matter of weeks, says Neurogen's vice president Charles Manly.

But pharmaceutical companies are seeking to do more than just increase the number of drugs they test: they are also looking for better ways to select the best drugs early in the process. One way they are doing this is by making early drug screening richer in information. Instead of just testing whether a compound can bind to a receptor, for instance, researchers are developing high-throughput assays to measure how strong the binding is and how the drug affects the various biochemical processes of a cell. Does it switch on the correct genes and proteins, for example, or does it shut them off? Testing a drug's selectivity, toxicity, metabolism and absorption at the start of the screening process will cut down on efforts wasted on trying ineffective drugs in humans.

LIVING CHIPS

Eventually, scientists will be able to assay compounds on living cells that are growing on silicon chips, says D. Lansing Taylor of Cellomics in Pittsburgh. He and his colleagues are now developing such a cell chip for detecting agents of biological warfare. The device, dubbed a "canary on a chip," is a prepackaged piece of silicon covered with living nerve cells from insects. Many of the bacteria believed to be favored by bioterrorists secrete nerve toxins, so these chips could provide an early warning of a biological attack.

Such cell-chip technology might also allow doctors to determine which kinds of chemotherapies would work best for a cancer patient. A physician could biopsy a tumor, grow the harvested cells on a chip and then test to see which chemicals would be most effective at killing the cells. Testing the cells themselves could save the patient from undergoing a series of unnecessary and ineffective treatments.

For some of these technologies, the future is already here. Affymetrix in Santa Clara, Calif., now offers a SNP chip that can be used to detect 18 variants of the gene that codes for cytochrome P450—a liver enzyme responsible for breaking down nearly one quarter of all commonly prescribed drugs. The company should soon release HuSNP, a DNA chip that will allow researchers or physicians to characterize genetic variations at 1,500 different marker sequences, which will help them link individual variations to different diseases. And in the next few years workers at the National Institutes of Health's National Human Genome Research Institute (NHGRI)—and at the 10 pharmaceutical companies that recently banded with the Wellcome Trust to form the SNP Consortium—expect to generate a map containing some 400,000 SNPs.

And that's when the fun will begin. "We'll have this catalogue of SNPs, but we'll still have to figure out which ones are associated with disease risk or drug response," says Francis S. Collins, director of the NHGRI. Then disease by disease, drug by drug, investigators will need to compare thousands of individuals—people who respond well to a drug and those who respond poorly, for example—and determine how they differ at every one of these 400,000 SNPs. "That's a lot of SNPs," Collins notes. But the potential benefits—to drug companies and to society—are sure to be greater than the considerable challenge.

PILLS OF TOMORROW: PAPER OR PLASTIC?

Sure, one milligram is fine for you. But your mom may need 10, and Grandpa can't get away with taking less than 100. How can pharmacies cater to the full range of needs that will arise once gene screening optimizes drug dosages for particular individuals?

The answer, according to one company, lies in the humble office photocopier. Researchers at Delsys in Princeton, N.J., are using electrostatic charges to deposit precise amounts of drugs onto sheets of gelatinlike polymer or even onto pieces of paper. The charge attracts and holds the dry powder—whether ink or drug—to the backing. "It's using a technology that's nearly 100 years old to address a 21st-century problem," says Martyn Greenacre, CEO of Delsys.

COURTESY OF DELSYS

One prescription for the future predicts that tablets and capsules won't be alone on pharmacy shelves. Dots of drugs sprayed on an edible backing could allow us to take just the amount we need and no more.

Someday medications for controlling abnormal heart rhythms might be shaped like little hearts on a strawberry-flavored polymer that just melts in your mouth. Although the image may call to mind the LSD microdots of the late 1960s, Greenacre hopes to avoid becoming known as the Timothy Leary of medical manufacturing. If the U.S. Food and Drug Administration approves the new method, these drug dots may hit the market by 2003.

Once Delsys gets the production process up to speed—they would like to be able to run off about 3,000 pills per minute—a doctor should be able to tap your prescription into his terminal and have the pharmacist print out your personalized paper pills lickety-split. —*K.H.*

ABOUT THE AUTHOR

KAREN HOPKIN is a freelance science writer who lives in suburban Washington, D.C. If she could carry her genes around on a credit card, she would undoubtedly lose it.

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GROWING NEW ORGANS

Researchers have taken the first steps toward creating semisynthetic, living organs that can be used as human replacement parts. **By David J. Mooney and Antonios G. Mikos**

EVERY DAY thousands of people of all ages are admitted to hospitals because of the malfunction of some vital organ. Because of a dearth of transplantable organs, many of these people will die. In perhaps the most dramatic example, the American Heart Association reports that only 2,300 of the 40,000 Americans who needed a new heart in 1997 got one. Lifesaving livers and kidneys likewise are scarce, as is skin for burn victims and others with wounds that fail to heal. It can sometimes be easier to repair a damaged automobile than the vehicle's driver because the former may be rebuilt using spare parts, a luxury that human beings simply have not enjoyed.

An exciting new strategy, however, is poised to revolutionize the treatment of patients who need new vital structures: the creation of man-made tissues or organs, known as neo-organs. In one scenario, a tissue engineer injects or places a given molecule, such as a growth factor, into a wound or an organ that requires regeneration. These molecules cause the patient's own cells to migrate into the wound site, turn into the right type of cell and regenerate the tissue. In the second, and more ambitious, procedure, the patient receives cells—either his or her own or those of a donor—that have been harvested previously and incorporated into three-dimensional scaffolds of biodegradable polymers, such as those used to make dissolvable sutures. The entire structure of cells and scaffolding is transplanted into the wound site, where the cells replicate, reorganize and form new tissue. At the same time, the artificial polymers break down, leaving only a completely natural final product in the body—a neo-organ. The creation of neo-organs applies the basic knowledge gained in biology over the past few decades to the problems of tissue and organ reconstruction, just as advances in materials science make possible entirely new types of architectural design.

Science-fiction fans are often confronted with the concept of tissue engineering. Various television programs and movies have pictured individual organs or whole people (or aliens) growing from a few isolated cells in a vat of some powerful nutrient. Tissue engineering does not yet rival these fictional presentations, but a glimpse of the future has already arrived. The creation of tissue for medical use is already a fact, to a limited extent, in hospitals across the U.S. These groundbreaking applications involve fabricated skin, cartilage, bone, ligament and tendon and make musings of "off-the-shelf" whole organs seem less than far-fetched.

Indeed, evidence abounds that it is at least theoretically possible to engineer large, complex organs such as livers, kidneys, breasts, bladders and intestines, all of which include many different kinds of cells. The proof can be found in any expectant mother's womb, where a small group of undifferentiated cells finds the way to develop into a complex individual with multiple organs and tissues with vastly different properties and functions. Barring any unforeseen impediments, teasing out the details of the process by which a liver becomes a liver, or a lung a lung, will eventually allow researchers to replicate that process.

A PINCH OF PROTEIN

Cells behave in predictable ways when exposed to particular biochemical factors. In the simpler technique for growing new tissue, the engineer exposes a wound or damaged organ to factors that act as proponents of healing or regeneration. This concept is based on two key observations, in bones and in blood vessels.

In 1965 Marshall R. Urist of the University of California at Los Angeles demonstrated that new, bony tissue would form in animals that received implants of powdered bone. His observation led to the isolation of the specific proteins (the bone morphogenetic proteins, or BMPs) responsible for this activity and to the determination of the DNA sequences of the relevant genes. A number of biotechnology companies subsequently began to produce large quantities of recombinant human BMPs; the genes

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GRANT JERDING

coding for BMPs were inserted into mammalian cell lines that then produced the proteins.

Various clinical trials are under way to test the ability of these bone growth promoters to regenerate bony tissue. Applications of this approach that are currently being tested include healing acute bone fractures caused by accidents and boosting the regeneration of diseased periodontal tissues. Creative BioMolecules in Hopkinton, Mass., recently completed clinical trials showing that BMP-7 does indeed help heal severe bone fractures. This trial followed 122 patients with leg fractures in which the sections failed to rejoin after nine months. Patients whose healing was encouraged by BMP-7 did as well as those who received a surgical graft of bone harvested from another part of their body.

A critical challenge in engineering neo-organs is feeding each and every cell. Tissues more than a few millimeters thick require blood vessels to grow into them and supply the necessary nutrients. Fortunately, investigations by Judah Folkman have shown that cells already in the body can be coaxed into producing new blood vessels. Folkman, a cancer researcher at Harvard Medical School's Children's Hospital, recognized this possibility almost three decades ago in studies aimed, ironically, at the prevention of cellular growth in the form of cancerous tumors.

Folkman perceived that developing tumors need to grow their own blood vessels to supply themselves with nutrients. In 1972 he proposed that specific molecules could be used to inhibit such vessel growth, or angiogenesis, and perhaps starve tumors. (This avenue of attack against cancer became a major news story in 1998.) Realizing that other molecules would undoubtedly abet angiogenesis, he and others have subsequently identified a number of factors in each category.

It is theoretically possible to **engineer organs** such as **livers, kidneys, breasts** and **intestines.**

That work is now being exploited by tissue engineers. Many angiogenesis-stimulating molecules are commercially available in recombinant form, and animal studies have shown that such molecules promote the growth of new blood vessels that bypass blockages in, for example, the coronary artery. Small-scale trials are also under way to test this approach in the treatment of similar conditions in human subjects.

Scientists must surmount a few obstacles, however, before drugs that promote tissue and organ formation become commonplace. To date, only the factors responsible for bone and blood vessel growth have been characterized. To regenerate other organs, such as a liver, for example, the specific molecules for their development must be identified and produced reliably.

An additional, practical issue is how best to administer the substances that would shape organ regeneration. Researchers must an-

The human body may be more than a sum of parts, but replacing failing parts should help to extend and improve life.

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PRASAD SHASTRI AND IVAN MARTIN *Massachusetts Institute of Technology*

Synthetic polymer scaffold in the shape of a nose (*left*) is "seeded" with cells called chondrocytes that replace the polymer with cartilage over time (*right*) to make a suitable implant.

swer these questions: What specific concentrations of the molecules are needed for the desired effect? How long should the cells be exposed? How long will the factors be active in the body? Certainly multiple factors will be needed for complex organs, but when exactly in the development of the organ does one factor need to replace another? Controlled drug-delivery technology such as transdermal patches developed by the pharmaceutical industry will surely aid efforts to resolve these concerns.

In particular, injectable polymers may facilitate the delivery of bioactive molecules where they are needed, with minimal surgical intervention. Michael J. Yaszemski of the Mayo Clinic, Alan W. Yasko of the M. D. Anderson Cancer Center in Houston and one of us (Mikos) are developing new injectable biodegradable polymers for orthopedic applications. The polymers are moldable, so they can fill irregularly shaped defects, and they harden in 10 to 15 minutes to provide the reconstructed skeletal region with mechanical properties similar to those of the bone they replace. These polymers subsequently degrade in a controlled fashion, over a period of weeks to months, and newly grown bone fills the site.

We have also been studying the potential of injectable, biodegradable hydrogels—gelatinlike, water-filled polymers—for treating dental defects, such as poor bonding between teeth and the underlying bone, through guided bone regeneration. The hydrogels incorporate molecules that both modulate cellular function and induce bone formation; they provide a scaffold on which new bone can grow, and they minimize the formation of scar tissue within the regenerated region.

An intriguing variation of more conventional drug delivery has been pioneered by Jeffrey F. Bonadio, Steven A. Goldstein and their co-workers at the University of Michigan. (Bonadio is now at Selective Genetics in San Diego.) Their approach combines the concepts of gene therapy and tissue engineering. Instead of administering growth factors directly, they insert genes that encode those molecules. The genes are part of a plasmid, a circular piece of DNA constructed for this purpose. The surrounding cells take up the DNA and treat it as their own. They turn into tiny factories, churning out the factors coded for by the plasmid. Because the inserted DNA is free-floating, rather than incorporated into the cells' own DNA, it eventually degrades and the product ceases to be synthesized. Plasmid inserts have successfully promoted bone regrowth in animals; the duration of their effects is still being investigated.

One of us (Mooney), along with Lonnie D. Shea and our other aforementioned Michigan colleagues, recently demonstrated with animals that three-dimensional biodegradable polymers spiked with plasmids will release that DNA over extended periods and simultaneously serve as a scaffold for new tissue formation. The DNA finds its way into adjacent cells as they migrate into the polymer scaffold. The cells then express the desired proteins. This technique makes it possible to control tissue formation more precisely; physicians might one day be able to manage the dose and time course of molecule production by the cells that take up the DNA and deliver multiple genes at various times to promote tissue formation in discrete stages.

A DASH OF CELLS

Promoting tissue and organ development via growth factors is obviously a considerable step forward. But it pales in comparison to the ultimate goal of the tissue engineer: the creation from scratch of whole neo-organs. Science fiction's conception of prefabricated "spare parts" is slowly taking shape in the efforts to transplant cells directly to the body that will then develop into the proper bodily component. The best way to sprout organs and tissues is still to rely on the body's own biochemical wisdom; the appropriate cells are transferred, in a three-dimensional matrix, to the desired site, and growth unfolds within the person or organism rather than in an external, artificial environment. This approach, pioneered by Ioannis V. Yannas, Eugene Bell and Robert S. Langer of the Massachusetts Institute of Technology, Joseph P. Vacanti of Harvard Medical School and others in the 1970s and 1980s, is now actually in use in some patients, notably those with skin wounds or cartilage damage.

The usual procedure entails the multiplication of isolated cells in culture. These cells are then used to seed a matrix, typically one consisting of synthetic polymers or collagen, the protein that forms the natural support scaffolding of most tissues. In addition to merely delivering the cells, the matrix both creates and main-

Sufficient knowledge of how **organs naturally develop** should eventually make true **"off-the-shelf" organs** a reality.

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ADVANCED TISSUE SCIENCES, INC.

Cartilaginous ear awaits a useful incarnation as a replacement body part. An ear-shaped polymer mold and cartilage-secreting cells enabled researchers to produce the "bioartificial" structure in the laboratory.

tains a space for the formation of the tissue and guides its structural development. Once the developmental rules for a given organ or tissue are known, any of those entities could theoretically be grown from a sample of starter cells. (A sufficient understanding of the developmental pathways should eventually allow the transfer of this procedure from the body to the laboratory, making true off-the-shelf organs possible. A surgeon could implant these immediately in an emergency situation—an appealing notion, because failing organs can quickly lead to death—instead of waiting weeks or months to grow a new organ in the laboratory or to use growth factors to induce the patient's own body to grow the tissues.)

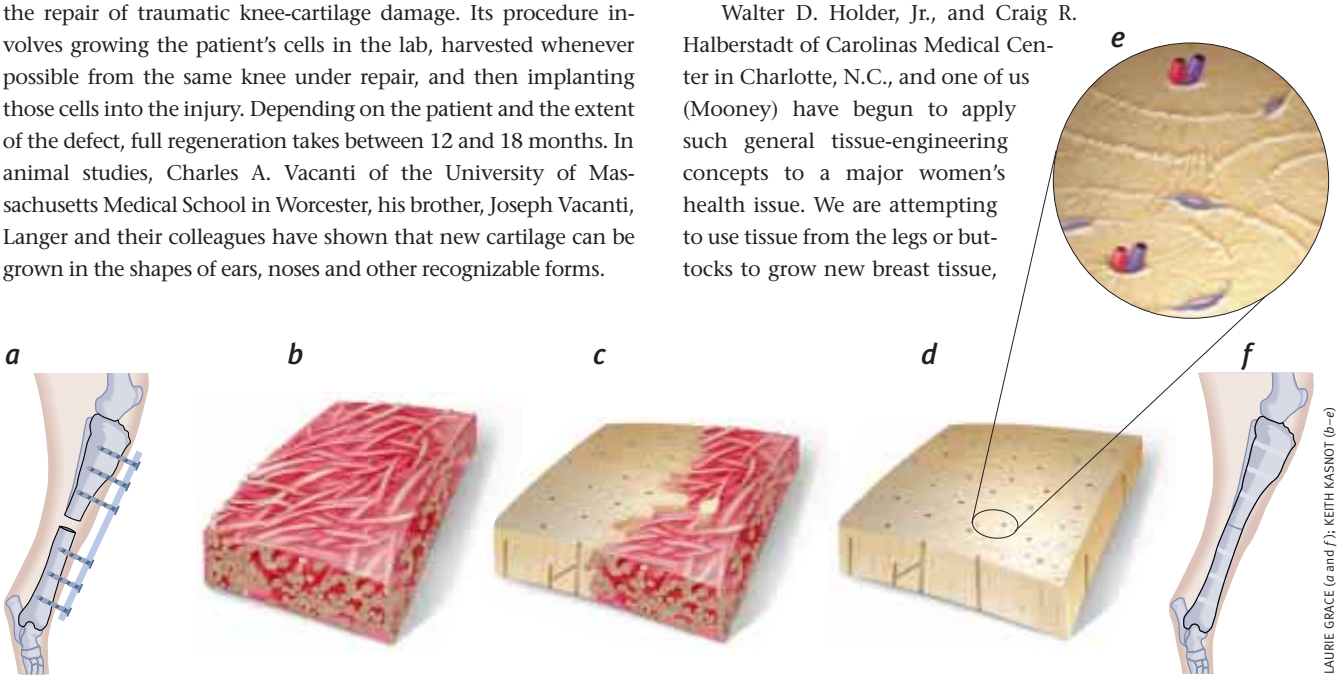
In the case of skin, the future is here. The U.S. Food and Drug Administration has already approved a living skin product—and others are now in the regulatory pipeline. The need for skin is acute: every year 600,000 Americans suffer from diabetic ulcers, which are particularly difficult to heal; another 600,000 have skin removed to treat skin cancer; and between 10,000 and 15,000 undergo skin grafts to treat severe burns.

The next tissue to be widely used in humans will most likely be cartilage for orthopedic, craniofacial and urological applications. Currently available cartilage is insufficient for the half a million operations annually in the U.S. that repair damaged joints and for the additional 28,000 face and head reconstructive surgeries. Cartilage, which has low nutrient needs, does not require growth of new blood vessels—an advantage for its straightforward development as an engineered tissue.

Genzyme Tissue Repair in Cambridge, Mass., has received FDA approval to engineer tissues derived from a patient's own cells for the repair of traumatic knee-cartilage damage. Its procedure involves growing the patient's cells in the lab, harvested whenever possible from the same knee under repair, and then implanting those cells into the injury. Depending on the patient and the extent of the defect, full regeneration takes between 12 and 18 months. In animal studies, Charles A. Vacanti of the University of Massachusetts Medical School in Worcester, his brother, Joseph Vacanti, Langer and their colleagues have shown that new cartilage can be grown in the shapes of ears, noses and other recognizable forms.

The relative ease of growing cartilage has led Anthony J. Atala of Harvard Medical School's Children's Hospital to develop a novel approach for treating urological disorders such as incontinence. Reprogenesis in Cambridge, Mass., which supports Atala's research, is testing whether cartilage cells can be removed from patients, multiplied in the laboratory and used to add bulk to the urethra or ureters to alleviate urinary incontinence in adults and bladder reflux in children. These conditions are often caused by a lack of muscle tone that allows urine to flow forward unexpectedly or, in the childhood syndrome, to back up. Currently patients with severe incontinence or bladder reflux may undergo various procedures, including complex surgery. Adults sometimes receive collagen that provides the same bulk as the cartilage implant, but collagen eventually degrades. The new approach involves minimally invasive surgery to deliver the cells and grow the new tissue.

Walter D. Holder, Jr., and Craig R. Halberstadt of Carolinas Medical Center in Charlotte, N.C., and one of us (Mooney) have begun to apply such general tissue-engineering concepts to a major women's health issue. We are attempting to use tissue from the legs or buttocks to grow new breast tissue,



LAURIE GRACE (*a* and *f*); KEITH KASNOT (*b*–*e*)

New bone grows to fill a space between two bone segments. A dog leg bone with a missing section is held in place with braces (*a*). A polymer scaffold primed with bone growth–promoting proteins (*b*) fills in the gap. The scaffold is slowly infiltrated by new bone (*c*) and ultimately gets completely replaced (*d*). The cells (*e*) have their own blood supply (*red and blue vessels*). After several months the leg bone has healed completely (*f*).

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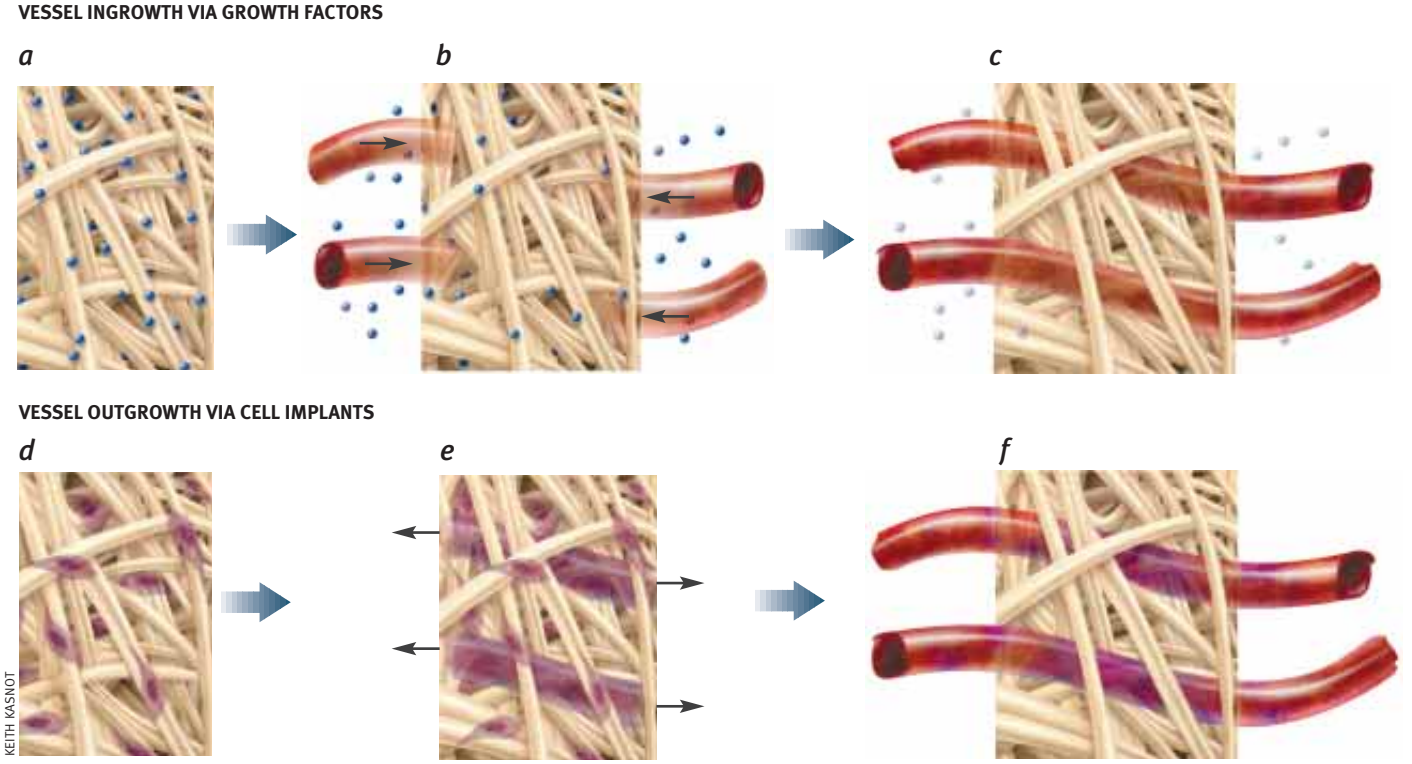

Vascularization of new, implanted tissue can be accomplished in two ways. Vessels from the surrounding tissue can be induced to infiltrate the tissue implant. Such vessel growth is promoted by including growth factors (*blue dots*) in the polymer scaffold of the insert (*a*). These factors diffuse into the local environment, where they encourage existing blood vessels to grow into the polymer (*b*). Ultimately, cells growing in from both sides knit together to form a continuous blood vessel (*c*). Vessels may also grow from within a polymer scaffold if that scaffold is seeded (*d*) with endothelial cells (*purple*). The cells will proliferate within the polymer matrix and grow outward toward the natural tissue (*e*). These new vessels combine with existing blood vessels (*red*) to create a continuous vessel (*f*).

to replace that removed in mastectomies or lumpectomies. We propose to take a biopsy of the patient's tissue, isolate cells from this biopsy and multiply these cells outside the body. The woman's own cells would then be returned to her in a biodegradable polymer matrix. Back in the body, cell growth and the deterioration of the matrix would lead to the formation of completely new, natural tissue. This process would create only a soft-tissue mass, not the complex system of numerous cell types that makes up a true breast. Nevertheless, it could provide an alternative to current breast prostheses or implants.

Optimism for the growth of large neo-organs of one or more cell types has been fueled by success in animal models of human diseases. Mikos has demonstrated that new bone tissue can be grown by transplanting cells taken from bone marrow and growing them on biodegradable polymers. Transplantation of cells to skeletal defects makes it possible for cells to produce factors locally, offering a new means of delivery for growth-promoting drugs.

RECIPES FOR THE FUTURE

In any system, size imposes new demands. As previously noted, tissues of any substantial size need a blood supply. To address that requirement, engineers may need to transplant the right cell types together with drugs that spur angiogenesis. Molecules that promote blood vessel growth could be included in the polymers used as transplant scaffolds. Alternatively, we and others have proposed that it may be possible to create a blood vessel network within an engineered organ prior to transplantation by incorporating cells that will become blood vessels within the scaffold matrix. Such engineered blood vessels would then need only to connect to surrounding vessels for the engineered tissue to develop a blood supply.

In collaboration with Peter J. Polverini of Michigan, Mooney has shown that transplanted blood vessel cells will indeed form such connections and that the new vessels are a blend of both implanted and host cells. But this technique might not work when transplanting engineered tissue into a site where blood vessels have been damaged by cancer therapy or trauma. In such situations, it may be necessary to propagate the tissue first at another site in the body where blood vessels can more readily grow into the new structure. Mikos collaborates with Michael J. Miller of the M. D. Anderson Cancer Center to fabricate vascularized bone for reconstructive surgery using this approach. A jawbone, for instance, could be grown connected to a well-vascularized hipbone for an oral cancer patient who has received radiation treatments around the mouth that damaged the blood supply to the jawbone.

On another front, engineered tissues typically use biomaterials

Skin, **bone** and **cartilage** are the **first success stories**. The holy grail of tissue engineering remains **complete internal organs**.

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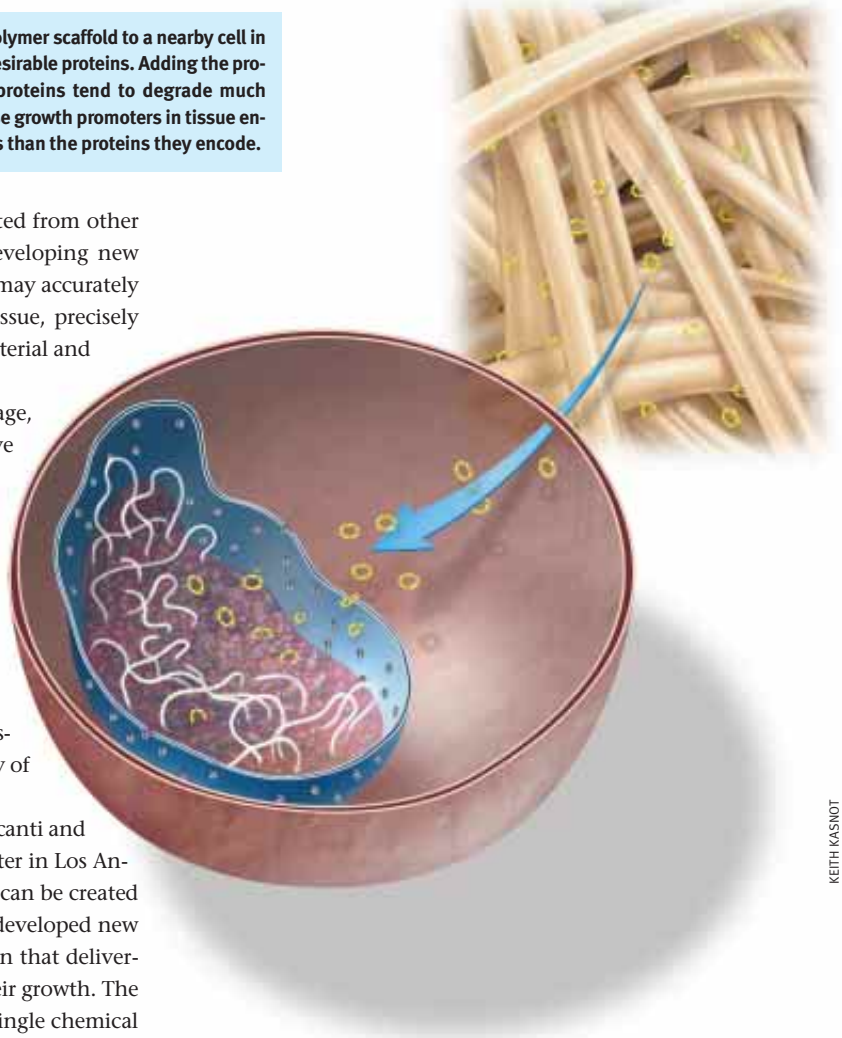

KEITH KASNOT

Plasmids, circlets of DNA (*yellow*), find their way from a polymer scaffold to a nearby cell in the body, where they serve as the blueprints for making desirable proteins. Adding the proteins themselves would be less effective because the proteins tend to degrade much faster than the plasmids do. Researchers attempting to use growth promoters in tissue engineering may thus find it more reliable to insert plasmids than the proteins they encode.

that are available from nature or that can be adapted from other biomedical uses. We and others, however, are developing new biodegradable materials specific to this task. These may accurately determine the size and shape of an engineered tissue, precisely control the function of cells in contact with the material and degrade at rates that optimize tissue formation.

Structural tissues, such as skin, bone and cartilage, will most likely continue to dominate the first wave of success stories, thanks to their relative simplicity. The holy grail of tissue engineering, of course, remains complete internal organs. The liver, for example, performs many chemical reactions critical to life, and more than 30,000 people die every year because of liver failure. It has been recognized since at least the time of the ancient Greek legend of Prometheus that the liver has the unique potential to regenerate partially after injury, and tissue engineers are now trying to exploit this property of liver cells.

A number of investigators, including Joseph Vacanti and Achilles A. Demetriou of Cedars-Sinai Medical Center in Los Angeles, have demonstrated that new liverlike tissues can be created in animals from transplanted liver cells. We have developed new biomaterials for growing liverlike tissues and shown that delivering drugs to transplanted liver cells can increase their growth. The new tissues grown in all these studies can replace single chemical functions of the liver in animals, but the entire function of the organ has not yet been replicated.

H. David Humes of Michigan and Atala are using kidney cells to make neo-organs that possess the filtering capability of the kidney. In addition, recent animal studies by Joseph Vacanti's group have demonstrated that intestine can be grown—within the abdominal cavity—and then spliced into existing intestinal tissue. Human versions of these neointestines could be a boon to patients suffering from short-bowel syndrome, a condition caused by birth defects or trauma. This syndrome affects physical development because of digestion problems and insufficient nutrient intake. The only available treatment is an intestinal transplant, although few patients actually get one, again because of the extreme shortage of donated organs. Recently Atala has also demonstrated in animals that a complete bladder can be formed with this approach and used to replace the native bladder.

Even the heart is a target for regrowth. A group of scientists headed by Michael V. Sefton at the University of Toronto recently began an ambitious project to grow new hearts for the multitude of people who die from heart failure every year. It will very likely take scientists 10 to 20 years to learn how to grow an entire heart, but tissues such as heart valves and blood vessels may be available sooner. Indeed, several companies, including Advanced Tissue Sciences in La Jolla, Calif., and Organogenesis in Canton, Mass., are attempting to develop commercial processes for growing these tissues.

Prediction, especially in medicine, is fraught with peril. A safe way to prophesy the future of tissue engineering, however, may be to weigh how surprised workers in the field would be after being told of a particular hypothetical advance. Tell us that completely functional skin constructs will be available for most medical uses within five years, and we would consider that reasonable. Inform us that fully functional, implantable livers will be here in five years, and we would be quite incredulous. But tell us that this same liver will be here in, say, 30 years, and we might nod our heads in sanguine acceptance—it sounds possible. Ten millennia ago the development of agriculture freed humanity from a reliance on whatever sustenance nature was kind enough to provide. The development of tissue engineering should provide an analogous freedom from the limitations of the human body.

ABOUT THE AUTHORS

DAVID J. MOONEY and ANTONIOS G. MIKOS have collaborated for eight years. Mooney has been on the faculty at the University of Michigan since 1994, where he is associate professor of biologic and materials sciences and of chemical engineering. Mikos is associate professor of bioengineering and of chemical engineering at Rice University. This article also appeared in *Scientific American* in April 1999.

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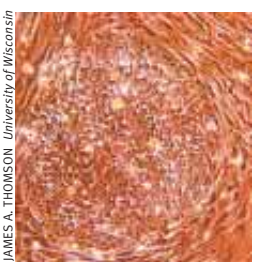
EMBRYONIC STEM CELLS FOR MEDICINE

Cells able to generate virtually all other cell types have recently been isolated. One day they could help repair a wide variety of damaged tissues. **By Roger A. Pedersen**

YOUR FRIEND has suffered a serious heart attack while hiking in a remote region of a national park. By the time he reaches a hospital, only one third of his heart is still working, and he seems unlikely to return to his formerly active life. Always the adventurer, though, he volunteers for an experimental treatment. He provides a small sample of skin cells. Technicians remove the genetic material from the cells and inject it into donated human eggs from which the nucleus, which houses the gene-bearing chromosomes, has been removed. These altered eggs are grown for a week in a laboratory, where they develop into early-stage embryos. The embryos yield cells that can be cultured to produce what are called embryonic stem cells. Such cells are able to form heart muscle cells, as well as other cell types.

The medical team therefore establishes a culture of embryonic stem cells and grows them under conditions that induce them to begin developing into heart cells. Being a perfect genetic match for your friend, these cells can be transplanted into his heart without causing his immune system to reject them. They grow and replace cells lost during the heart attack, returning him to health and strength.

This scenario is for now hypothetical, but it is not fantastic. Researchers already know of various types of stem cells. These are not themselves specialized to carry out the unique functions of particular organs, such as the heart, the liver or the brain. But when stem cells divide, some of the progeny "differentiate"—that is, they undergo changes that commit them to mature into cells of specific types. Other progeny remain as stem cells. Thus, intestinal stem cells continually regenerate the lining of the gut, skin stem cells make skin, and hematopoietic stem cells give rise to the range of cells found in blood. Stem cells enable our bodies to repair everyday wear and tear.



JAMES A. THOMSON *University of Wisconsin*

Human embryonic stem cells growing in culture (*central clump*) are maintained on a layer of mouse "feeder" cells (*background*).

Embryonic stem cells are even more extraordinary: they can give rise to essentially all cell types in the body. Human embryonic stem cells were first grown in culture just last year. In February 1998 James A. Thomson of the University of Wisconsin found the first candidates when he noted that certain human cells plucked from a group growing in culture resembled embryonic stem cells that he had earlier derived from rhesus monkey embryos. A thousand miles away in Baltimore, John D. Gearhart of Johns Hopkins University was isolating similar cells by culturing fragments of human fetal ovaries and testes. And in California, researchers at Geron Corporation in Menlo Park and in my laboratory at the University of California at San Francisco were carrying out related studies.

But Thomson was well served by his previous experience with embryonic stem cells of rhesus monkeys and marmosets, which—like humans—are primates. In the following months he pulled ahead of the rest of us in the difficult task of inducing the fragile human cells to grow in culture, and he confirmed that they were indeed embryonic stem cells.

FAR-REACHING POTENTIAL

In studies reported in the November 6, 1998, issue of *Science*, Thomson demonstrated that the human cells formed a wide variety of recognizable tissues when transplanted under the skin of mice. Discussing his results before an inquisitive subcommittee of the U.S. Senate, Thomson described how the cells gave rise to tissue like that lining the gut as well as to cartilage, bone, muscle and neural epithelium (precursor tissue of the nervous system), among other types. What is more, descendants of all three fun-

CYNTHIA TURNER

Cultured cells that have been derived from early human embryos may eventually be coaxed to develop into replacement tissue for a variety of damaged organs, including the heart.

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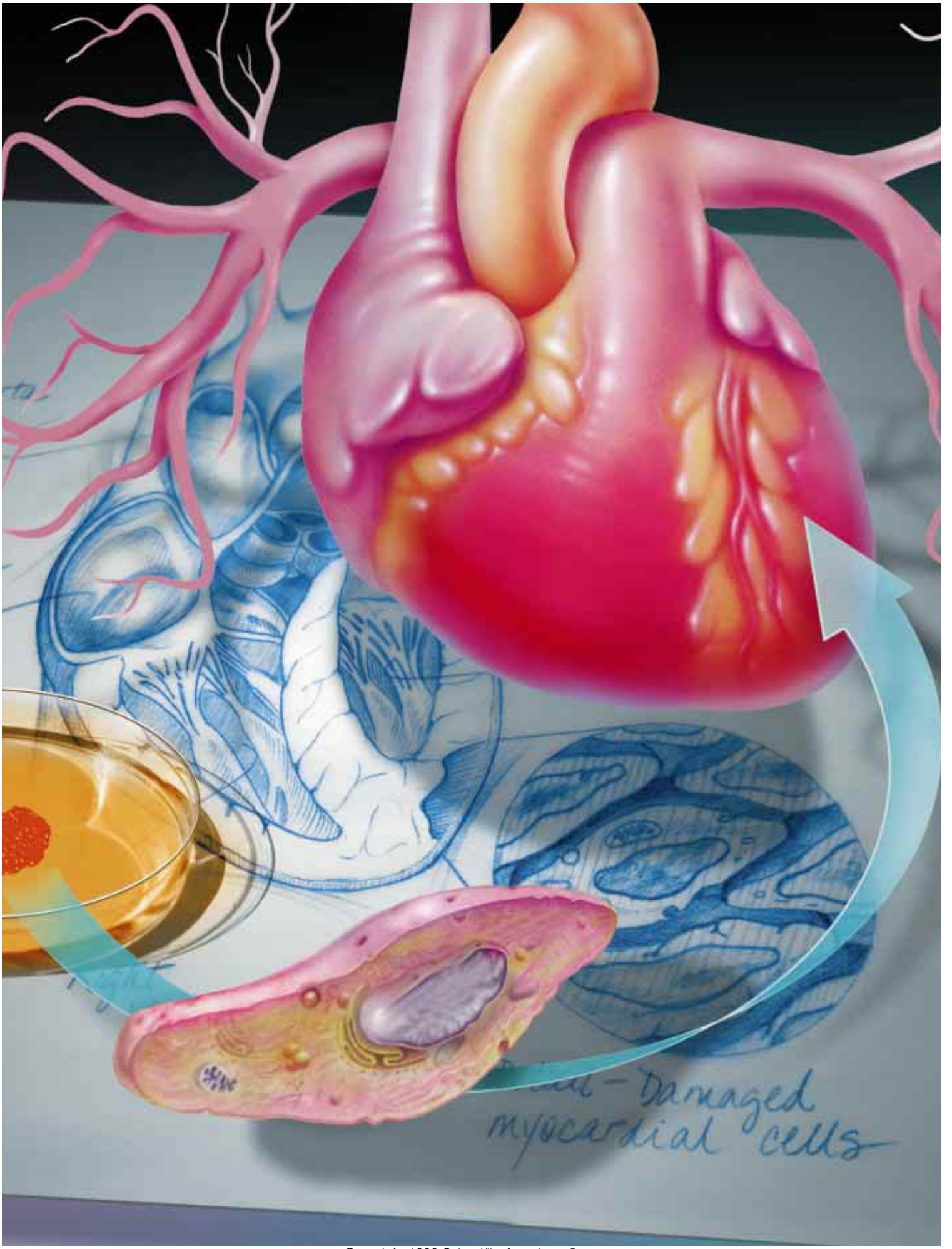

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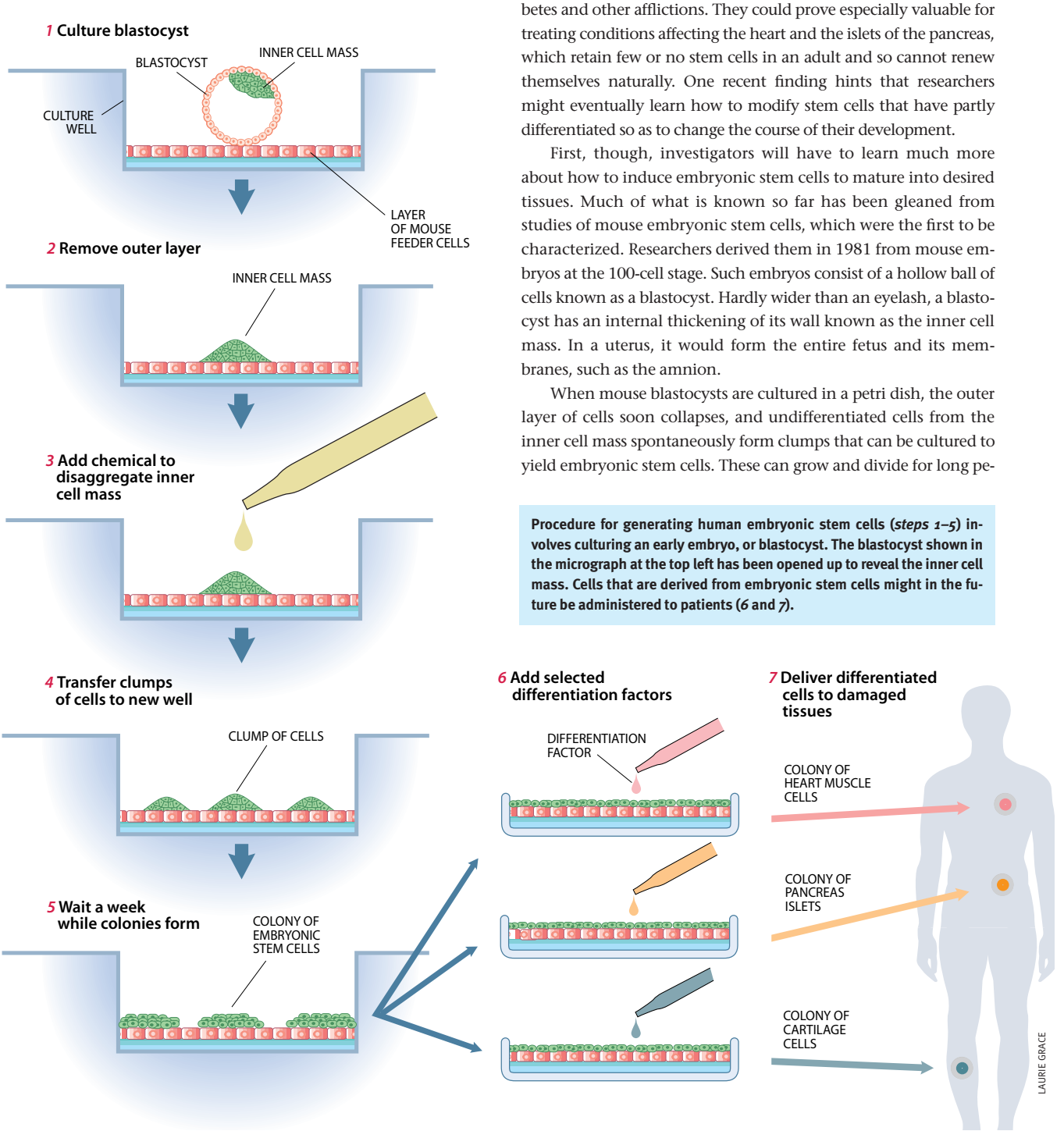
YORGOS NIKAS, *Hammersmith Hospital, London*

damental body layers of a mammalian embryo were represented. Some normally derive from the outermost layer (the ectoderm), others from the innermost or middle layers (the endoderm or mesoderm). This variety offered further evidence of the cells' developmental flexibility. Such results encourage hope that research on embryonic stem cells will ultimately lead to techniques for generating cells that can be employed in therapies for many conditions in which tissue is damaged.

If it were possible to control the differentiation of human embryonic stem cells in culture, the resulting cells could help repair damage caused by congestive heart failure, Parkinson's disease, diabetes and other afflictions. They could prove especially valuable for treating conditions affecting the heart and the islets of the pancreas, which retain few or no stem cells in an adult and so cannot renew themselves naturally. One recent finding hints that researchers might eventually learn how to modify stem cells that have partly differentiated so as to change the course of their development.

First, though, investigators will have to learn much more about how to induce embryonic stem cells to mature into desired tissues. Much of what is known so far has been gleaned from studies of mouse embryonic stem cells, which were the first to be characterized. Researchers derived them in 1981 from mouse embryos at the 100-cell stage. Such embryos consist of a hollow ball of cells known as a blastocyst. Hardly wider than an eyelash, a blastocyst has an internal thickening of its wall known as the inner cell mass. In a uterus, it would form the entire fetus and its membranes, such as the amnion.

When mouse blastocysts are cultured in a petri dish, the outer layer of cells soon collapses, and undifferentiated cells from the inner cell mass spontaneously form clumps that can be cultured to yield embryonic stem cells. These can grow and divide for long pe-


1 Culture blastocyst
BLASTOCYST
INNER CELL MASS
CULTURE WELL
LAYER OF MOUSE FEEDER CELLS
2 Remove outer layer
INNER CELL MASS
3 Add chemical to disaggregate inner cell mass
4 Transfer clumps of cells to new well
CLUMP OF CELLS
5 Wait a week while colonies form
COLONY OF EMBRYONIC STEM CELLS
6 Add selected differentiation factors
DIFFERENTIATION FACTOR
7 Deliver differentiated cells to damaged tissues
COLONY OF HEART MUSCLE CELLS
COLONY OF PANCREAS ISLETS
COLONY OF CARTILAGE CELLS
LAURIE GRACE

Procedure for generating human embryonic stem cells (*steps 1–5*) involves culturing an early embryo, or blastocyst. The blastocyst shown in the micrograph at the top left has been opened up to reveal the inner cell mass. Cells that are derived from embryonic stem cells might in the future be administered to patients (*6* and *7*).

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riods in an undifferentiated state. Yet when injected back into a mouse blastocyst, they respond to physiological cues, and mature cells derived from those stem cells appear in virtually the full range of the embryo's tissues. For this reason embryonic stem cells are termed pluripotent, from the Latin for "many capabilities." (Mouse embryonic stem cells are sometimes described as totipotent, implying that they can form all tissues, although they do not form placenta.) Embryonic stem cells thus have a lot in common with cells in the inner cell mass, the mothers of all cells in the body, but are not identical to them: subtle changes occur in culture that slightly limit their potential.

As investigators experimented with different culture conditions, they found that if a key biological chemical, known as leukemia inhibitory factor, is not supplied, the cells start differentiating in an unpredictable way. Interestingly, though, the repertoire of cell types that have arisen in this way is much smaller than that seen when the cells are injected into a blastocyst—probably because vital biological chemicals present in the embryo are not in the culture medium. This contrast raised the question of whether artificial conditions could be found that would mimic those in the embryo.

DIRECTING DEVELOPMENT

Such manipulations are possible. Gerard Bain and David I. Gottlieb and their associates at the Washington University School of Medicine have shown that treating mouse embryonic stem cells with the vitamin A derivative retinoic acid can stimulate them to produce neurons (nerve cells). That simple chemical seems to achieve this dramatic effect on the cells by activating a set of genes used only by neurons while inhibiting genes expressed in cells differentiating along other pathways.

My colleague Meri Firpo and her former co-workers in Gordon Keller's laboratory at the National Jewish Medical and Research Center in Denver had comparable success deriving blood cells. They discovered that specific growth factors stimulated cells derived from embryonic stem cells to produce the complete range of cells found in blood.

Embryonic **stem cells** can give rise to **essentially all cell types** in the body.

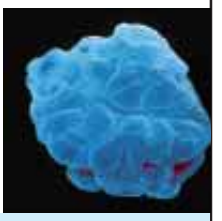
Embryonic stem cells might even generate some useful tissues without special treatment. I never cease to be amazed, when looking through a microscope at cultures derived from embryonic stem cells, to see spontaneously differentiating clumps beating with the rhythm of a heart. Investigators could potentially allow such transformations to occur and then select out, and propagate, the cell types they need.

Loren J. Field and his associates at the Indiana University School of Medicine have done just that. Employing a simple but elegant method, they enriched the yield of spontaneously differentiating heart muscle cells, or cardiomyocytes, to greater than 99 percent purity. To achieve that goal, they first introduced into mouse embryonic stem cells an antibiotic-resistance gene that had

THE ETHICS OF USING EMBRYONIC CELLS

THE FULL POTENTIAL of recent discoveries on embryonic stem cells will be realized only if society deems this research worthy of support. Many people feel that human embryos growing in laboratory dishes, even at the earliest stages of development (between fertilization and the 100-cell blastocyst stage), warrant special moral consideration, because they can grow into human beings if returned to a uterus for gestation. In 1994 an expert panel of ethicists and researchers convened by the U.S. National Institutes of Health studied the issue. It recommended that some embryo research, including the derivation and analysis of human embryonic stem cells, was ethically justifiable and merited consideration for federal funding.

Even so, a congressional ban has ensured that no federal monies have yet been appropriated for research on human embryos. (The work of James A. Thomson and John D. Gearhart mentioned in this article, as well as my own work on related cells, was all supported by Geron Corporation in Menlo Park, Calif.) Some countries, notably the U.K., have concluded that research on human embryos does warrant governmental review and support, whereas a few, such as Germany, have decided otherwise.



JASON BURNS *Phototake*

A human embryo five days after fertilization.

Together with most of my colleagues, I consider laboratory research on human embryos a legitimate scientific activity because of the work's enormous medical promise. Of course, informed consent must be obtained from the donors of any human materials used for research. Embryos are now routinely created in clinics to treat infertility, and those not implanted in a uterus are destroyed if they are not donated for research.

The transfer of experimental embryos to a uterus, however, must meet a different standard of ethics and safety, because that act opens up their potential to develop into human beings. Any manipulations on an embryo that is to develop must be demonstrably safe and bring unambiguous benefits for the resulting person.

It is clear that cloning human beings would not meet this standard, and I seriously doubt that it ever will. [*Editors' note:* Others disagree. See "I, Clone," on page 80.] That is why I spearheaded a voluntary moratorium on reproductive cloning of humans, a policy that has been endorsed by essentially all U.S. scientists who could credibly consider such an activity.

Early this year the NIH announced that it favors supporting research on lines of embryonic stem cells that scientists establish using funds from other sources. It did so after considering the biological potential of these cells. Once they are derived, either from a natural embryo or possibly from one produced through somatic cell nuclear transfer (as described in the main text), embryonic stem cells are no longer equivalent to an embryo in their developmental power.

Specifically, to grow stem cells in the test tube, researchers must remove the outer layer of cells in the originating blastocyst. These excised cells are essential to the development of the placenta, which normally nourishes the product of conception and protects it from rejection by the mother's immune system. By stripping them away, a researcher eliminates any possibility that the remaining inner cells can develop in a uterus. Embryonic stem cells provide a source of medically useful differentiating tissues that lack the awesome potential of an intact embryo. —*R.A.P.*

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Researchers should be able to make perfectly **matched tissues** for **transplantation.**

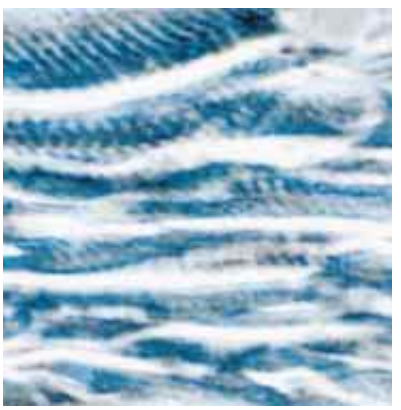
been engineered to express itself only in cardiomyocytes. After allowing the cells to differentiate and exposing them to enough antibiotic to kill cells that lacked the resistance gene, Field's team was able to recover essentially pure cardiomyocytes. Remarkably, when the cells were transplanted into the hearts of adult mice, the cardiomyocytes engrafted and remained viable for as long as seven weeks, the longest period the researchers analyzed.

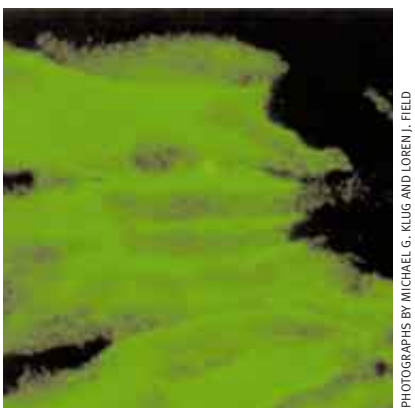
Likewise, Terrence Deacon of Harvard Medical School and his co-workers have transplanted embryonic stem cells into a particular region in the brains of adult mice. They observed that many of the engrafted cells assumed the typical shape of neurons. Some of those cells produced an enzyme that is needed to make the neurotransmitter dopamine and occurs in quantity in dopamine-secreting neurons. Others produced a chemical found in a different class of neurons. What is more, the nervelike cells in the grafts elaborated projections that resembled the long, signal-carrying neuronal branches known as axons; in the brain, some of these extended into the surrounding tissue. Whether such cells not only look normal but also function normally has not yet been assessed. Nor is it clear which (if any) growth factors in the mice stimulated the transplants to form neurons: surprisingly, nervelike cells also developed in grafts placed adjacent to the kidney.

The technique for establishing a culture of embryonic stem cells is more involved when primate embryos are the source, rather than mouse embryos. The outer cell layer of the primate blastocyst does not fall apart so readily in culture, so researchers must remove it, or the cells of the inner cell mass will die. But the results from the mouse studies suggest that as researchers gain experience with human embryonic stem cells, it will become possible to stimulate them to produce, at least, blood cells, heart muscle cells and neurons. Other medically valuable types might be achievable, such as pancreatic islet cells, for treatment of diabetes; skin fibroblasts, for treatment of burns or wounds; chondrocytes, for regenerating cartilage lost in arthritis; and endothelial (blood vessel–forming) cells, to repair blood vessels damaged by atherosclerosis.

Unfortunately, embryonic stem cells also have a dark side. The jumble of cell types they form when injected into mature mice constitutes a type of tumor, known as a teratoma. Researchers will have to be sure, before using cells therapeutically, that they have all differentiated enough to be incapable of spreading inappropriately or forming unwanted tissue. Rigorous purification of such cells will be required to safeguard the recipients.

The cells that Gearhart obtained from developing ovaries and testes also show medical promise. They are called embryonic germ cells, because they are derived from the ancestors of sperm and eggs, which are together referred to as germ cells. Gearhart has shown that his cells, too, are pluripotent: in the petri dish they can give rise to cells characteristic of each of the embryo's basic layers. As of this writing, however, Gearhart has not published details of what happens when embryonic germ cells are placed under the skin of mice, so information about their potential for tissue formation is still somewhat limited.





PHOTOGRAPHS BY MICHAEL G. KLUG AND LOREN J. FIELD *Indiana University School of Medicine*

Myosin, a protein found mainly in muscle, fluoresces red in cells derived from mouse embryonic stem cells (*left*). Transplanted into a mouse's heart, the cells become enmeshed with heart muscle (*center*). The donated cells can be distinguished by green fluorescence (*right*).

CHALLENGES AND OPPORTUNITIES

All the differentiated cells discussed so far would probably be useful in medicine as isolated cells or as suspensions; they do not have to organize themselves into precisely structured, multicellular tissues to serve a valuable function in the body. That is good news, because organ formation is a complex, three-dimensional process. Organs generally result from interactions between embryonic tissues derived from two distinct sources. Lungs, for example, form when cells derived from the middle layer of the embryo interact with those of the embryonic foregut, which is derived from the inner layer. The process stimulates embryonic foregut cells to form branches that eventually become the lungs. For would-be tissue engineers, learning how to direct pluripotent stem cells through similar interactions with the goal of building entire organs will be

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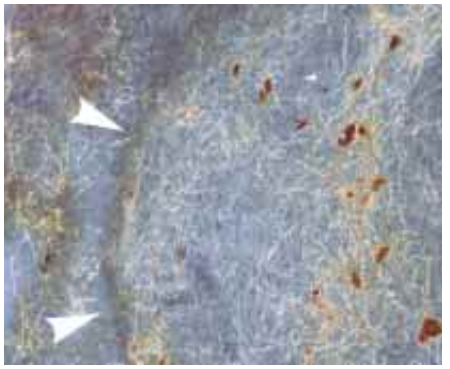

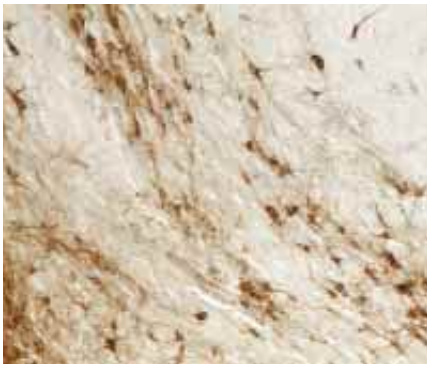

TERRENCE DEACON *Harvard Medical School*

Cells resembling nerve cells (*brown and gold in image at right*) form when mouse embryonic stem cells are placed in a mouse brain (*blue background*). Indications that the cells may indeed be nerve cells include the extension of projections into the surrounding tissue (*arrows*) and the production of an enzyme (*brown in far right image*) made by certain nerve cells in the brain.

hugely difficult. Nevertheless, some researchers are working on solutions to those very problems.

Another challenge is to create cells for transplantation that are not recognized as foreign by the recipient's immune system. This end could be achieved in principle by genetically altering human embryonic stem cells so they function as "universal donors" compatible with any recipient. Alternatively, embryonic stem cells genetically identical to the patient's cells could be created, as in the scenario of the heart attack victim described earlier.

The first option, creating a universal donor cell type, would involve disrupting or altering a substantial number of genes in cells. The changes would prevent the cells from displaying proteins on their outer surface that label them as foreign for the immune system. Yet bringing about this alteration could be hard, because it would require growing embryonic stem cells under harsh conditions, in particular exposing them to multiple rounds of selection with different drugs.

The second option, making cells that are genetically identical to the patient's tissues, involves combining embryonic stem cell technology and a fundamental step in cloning, as described in the vignette opening this article. Using a hollow glass needle one tenth of the diameter of a human hair, a researcher would transfer a somatic (nonreproductive) cell—or just its gene-containing nucleus—into an unfertilized egg whose chromosomes have been removed. The egg would then be activated by an electrical shock, launching it on its developmental journey with only the genetic information of the transferred, or donor, cell.

In several animal studies on nuclear transfer, cells from existing adult animals have been used as the gene donors, and the altered cells have been implanted into the uterus of a living animal. These experiments gave rise to Dolly the sheep and to some mice and cattle as well. To create cells for transplantation with this combination of approaches, an investigator would use a cell from the patient as a donor but would culture the resulting embryo only until it reached the blastocyst stage. Then the embryo would be used to produce embryonic stem cells that were genetically identical to a patient's own cells.

Human embryonic stem cells could have other applications, too. Because the cells could generate human cells in basically unlimited amounts, they should be extremely useful in research efforts designed for discovering rare human proteins. These programs need great quantities of cells in order to produce identifiable amounts of normally scarce proteins. And because embryonic stem cells resemble cells in early embryos, they could be employed to flag drugs that might interfere with development and cause birth defects.

Finally, such cells offer an approach to studying the earliest events in human development at the cellular and molecular levels in a way that is ethically acceptable. The moral issues associated with experiments on embryos should not arise because embryonic stem cells lack the ability to form an embryo by themselves [*see box on page 21*]. Research on the cells could provide insights into fundamental questions that have puzzled embryologists for decades, such as how embryonic cells become different from one another, and what causes them to organize into organs and tissues. The lessons learned from mice, frogs, fish and fruit flies on these subjects are highly germane to humans. Yet understanding these processes in our own species will ultimately provide us with the greatest benefits and the deepest satisfaction.

As **researchers** gain experience with **human embryonic stem cells**, it will become possible to stimulate them to produce, at least, blood cells, **heart muscle cells** and neurons.

ABOUT THE AUTHOR

ROGER A. PEDERSEN is professor of obstetrics, gynecology and reproductive sciences at the University of California, San Francisco. His moratorium on cloning of human beings can be read at www.faseb.org/opar/cloning.moratorium.html on the World Wide Web. This article also appeared in *Scientific American* in April 1999.

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HEAD TRANSPLANTS

Equipping old minds with new bodies—whether you call it head transplantation or body transplantation—is not outside science's ken. How would it work? **By Robert J. White**

LIVERS, LUNGS, hearts, kidneys…and, most recently, hands. With such rapid advances in the field of human transplantation, researchers such as myself are now beginning to consider what some have previously deemed unthinkable: transplanting a human brain.

I predict that what has always been the stuff of science fiction—the Frankenstein legend, in which an entire human being is constructed by sewing various body parts together—will become a clinical reality early in the 21st century. Our modern-day version of the tale will include the transplantation of the human brain with all its complexity preserved. But the brain can't function properly without the plumbing of the body and the wiring of the head. So brain transplantation, at least initially, will really be head transplantation—or body transplantation, depending on your perspective.

The concept of head transplantation has always held a certain fascination for experimental surgeons. As early as 1908, American physiologist and pharmacologist Charles C. Guthrie grafted the head of a small mixed-breed dog onto the neck of a larger one whose own head remained intact. Similarly, in the 1950s Russian scientist Vladimir P. Demikhov transplanted the upper body of a mixed-breed puppy—including the forelimbs—to the neck of a much larger dog by connecting the pup to the other dog's neck blood vessels. At least one of Demikhov's famous "two-headed dogs" reportedly survived as long as 29 days after the surgery.

It was not until 1970, however, that a mammalian head was successfully transplanted onto a mammalian body that had already had its own head removed. This was first accomplished by my colleagues and me in a nonhuman primate—a rhesus monkey. When the monkey awakened from anesthesia, it regained full consciousness and complete cranial nerve function, as measured by its wakefulness, aggressiveness, and ability to eat and to follow people moving around the room with its eyes. Such monkeys lived for as long as eight days. With the significant improvements in surgical techniques and postoperative management since then, it is now possible to consider adapting the head-transplant technique to humans.

A surgical protocol for head transplantation in humans would require very little alteration from that used in monkeys, although it would need to be scaled up because of the difference in body size between the two species. In fact, the procedure would be easier to perform in humans than in monkeys, because the blood vessels and other tissues of a human are larger than those of a monkey, and surgeons have much more experience operating on the human anatomy.

Maintaining an adequate, uninterrupted flow of blood to the brain would be absolutely essential during all stages of a human head-transplant operation because the brain, unlike other solid organs, cannot survive being separated from its blood supply (at least at normal body temperature). Surgeons would monitor the brain's activity—an indirect way to assess blood flow—during the procedure using electroencephalograph electrodes placed on the scalp. Each patient's head would also be placed in a circular clamp to allow it to be stabilized and moved safely.

HEADS OFF TO YOU

The procedure would be conducted in a specially designed operating suite that would be large enough to accommodate equipment for two operations conducted simultaneously by two separate surgical teams. Once the two patients were anesthetized, the two teams, working in concert, would make deep incisions around each patient's neck, carefully separating all the tissues and muscles to expose the carotid arteries, jugular veins and spine. The sur-

PHOTOGRAPHS BY JUSTINE PARSONS

Are we ready for head transplantation? The technology to carry out the procedure in humans already exists.

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My colleagues and **I have already taken** the **first steps** toward **human head transplantation.**

It's not beyond science's reach to put someone's head on a new body. The surgical procedure could prolong the lives of people who have been paralyzed.

geons would then place catheters coated with heparin, a drug that prevents blood clotting, into each of the blood vessels to ensure that the brain received sufficient blood flow and, therefore, oxygen. After removing bone from the spine of each patient's neck, they would cut open the protective membranes surrounding the spinal cord, exposing it. Following separation of the spine and cord, the head of one patient would be removed and transferred to the tubes that would connect it to the circulation of the second patient's body, which would have had its own head removed.

Once this critical maneuver was completed, the blood vessel tubes would be removed one by one, and the surgeons would sew the arteries and veins of the transplanted head together with those of the new body. The spinal columns would then be fastened together with metal plates, and the muscles and skin would be sewn together layer by layer.

My colleagues and I have already taken the first steps toward human head transplantation. We have developed pumps and devices to lower to 10 degrees Celsius (50 degrees Fahrenheit) the blood circulating to the head that is being prepared for transplantation. Such cooling slows the metabolism of the brain so that its blood supply can be cut off for up to an hour during surgery. The greatest hurdle remaining is how to prevent the body from rejecting the new head, and vice versa. It is unclear at this point whether the drugs now used to prevent rejection following transplantation of organs such as livers and kidneys will work for an entire body.

LONGER LIFE FOR THE PARALYZED?

Who might benefit from a head transplant? The first candidates for the procedure will probably be people who have been paralyzed from the neck down because of an accident. For reasons that are still unclear, such individuals often die prematurely of multiple-organ failure. Although transferring a paralyzed person's head to another body would not—at least at this point in the development of the technology—allow them to move or walk again, it could prolong their life. And many hope that in the 21st century, physicians will find a way to heal severed spinal cords, so those who have their heads transplanted onto a new body might someday receive sensory information from and gain motor control over it.

Where will bodies for head transplantation come from? The recipient body would be someone who has been declared brain dead. Such individuals already serve as multiple-organ donors, so there should be no strikingly new bioethics considerations for head transplantation.

But how well will we as a society accept the concept that human brain transplantation involves transplanting the mind and spirit? Are we willing to acknowledge that the human brain is the physical repository of the soul, something this operation implies? These are the questions facing us as we go in reality where Mary Wollstonecraft Shelley went only in fiction.

ABOUT THE AUTHOR

ROBERT J. WHITE is professor of neurosurgery at Case Western Reserve University. He prefers his own head (brain) for now.

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MUSCULAR AGAIN

Within a decade or two, scientists will create a genetic vaccine that increases muscle mass—without exercise. **By Glenn Zorpette**

IF PHYSICAL BEAUTY is an evanescent mélange, its foundation—a set of firm, shapely muscles—is just as fleeting. Bright, limpid eyes, good facial structure and lustrous hair can all persist, but muscles eventually wane.

Regular exercise can slow the decline quite a bit, and the rate of loss varies from person to person. Still, if you manage to be a healthy septuagenarian, chances are you will have lost at least 20 percent—and perhaps as much as one third—of the muscle mass you had in your late 20s.

Unfortunately for you, far more than your animal magnetism is at stake as your precious thews wither like a praying mantis in a pottery kiln. Muscle is the most abundant tissue in your body, which makes it the largest store of a variety of key substances. These include amino acids, the building blocks of the proteins that make up the struts and girders of cells and, in the form of enzymes, carry out the biochemical processes of life. For this reason, among others, the loss of muscle can actually weaken your immune system. Geriatric health specialists now also see muscle loss as underlying many of the injuries to elderly people caused by falling. Thrown off balance, an older person may not have the muscle power necessary to correct posture quickly enough to avoid a nasty fall.

With relatively few old-timers showing an inclination to pump iron three times a week for the rest of their lives, the potential market for an alternative muscle-building drug is clearly enormous. And science finally appears close to creating one. In separate experiments over the past couple of years at the University of Pennsylvania Medical Center in Philadelphia and at the Royal Free and University College Medical School in London, researchers tested muscle-building vaccines based on engineered genes. Injected into mice, the vaccines boosted muscle mass in the animals' legs by 15 to 27 percent. Amazingly, the increases were measurable in only a month or so and didn't require any exercise at all.

Lest couch potatoes rejoice, several major obstacles would have to be overcome before injections let inactive senior citizens go from park benches to bench presses. Still, many muscle researchers believe that human tests are inevitable, and some think the first ones will occur within the next couple of years. Not only would such a vaccine be about as close as humanity is likely to come anytime soon to an antiaging elixir, but it could also be a major breakthrough for the treatment of a host of degenerative muscle diseases, including the various forms of muscular dystrophy.

Genetic muscle-building **vaccines** would be **essentially undetectable** in the body.

On the downside, it takes little imagination to see the possibilities for abuse of the vaccines by healthy young athletes in power sports like football, sprinting and short-distance swimming. Compared with anabolic steroids, the modern-day illegal but ubiquitous muscle-building drug of choice, a vaccine based on an engineered gene would offer some major advantages. It would need to be administered only one time, rather than periodically, and it would be essentially undetectable in the body.

The mere likelihood of a muscle-building drug with those features is already causing anxiety in international sports circles. "When you come to a method where you are increasing proteins in the cells genetically and directly, you'll have to have much more sophisticated detection techniques," says Mats Garle, scientific director of the Doping Control Laboratory of Huddinge University

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Hospital in Sweden. The laboratory, which tests elite athletes, is one of the best of its kind in the world. "Maybe we'll never get a solution to that problem," Garle concedes.

MUSCLES 101

Muscle is among the strangest tissues in the human body. A single muscle cell consists of a membrane, many scattered nuclei that contain genes, and thousands of inner strands called myofibrils that constitute the cytoplasm of the cell. Sustained by the multiple nuclei, the cells can grow to be centimeters long.

Filling the inside of a muscle fiber, the myofibrils can be as long as the fiber and are the part that enables the cell to contract forcefully in response to nerve impulses. The actual contraction is accomplished by the myofibrils' tiny component units, which are called sarcomeres. They are linked end to end to make up a myofibril, which contracts when all of its sarcomeres do. Within each sarcomere are two filamentary proteins, called myosin and actin, whose interaction causes contraction. Basically, during contraction, a sarcomere shortens like a collapsing telescope, as the actin filaments at each end of a central myosin filament slide toward the myosin's center [see "The Mystery of Muscle," by Glenn Zorpette; SCIENTIFIC AMERICAN PRESENTS: Men: The Scientific Truth about Their Work, Play, Health and Passions, Summer 1999].

Muscle cells, also known as fibers, cannot split themselves to form completely new fibers. So a muscle can become more massive only when its individual fibers become thicker.

What causes this thickening is the creation of new myofibrils. In an extremely complex process that is still poorly understood, the mechanical stresses that exercise exerts on tendons and other structures connected to the muscle trigger many different biochemical pathways that ultimately cause the muscle cells to make more proteins. Enormous amounts of these proteins, chiefly myosin and actin, are needed as the cell produces additional myofibrils.

To produce and support all this protein requires more nuclei. As muscle cells cannot divide, the new nuclei are donated by so-called satellite cells, which are scattered among the many nuclei on the surface of a skeletal muscle fiber. Satellite cells are largely separate from the muscle cell and, unlike it, have only the usual one nucleus apiece. Thus, they can replicate by dividing.

Researchers now know that satellite cells proliferate in response to the stresses and wear and tear of exercise. As they multiply, some remain as satellites on the fiber, but others become incorporated into it. Their nuclei become indistinguishable from the muscle cell's other nuclei. With these additional nuclei, the fiber is able to churn out more proteins and create more myofibrils.

According to the prevailing theory, rigorous exercise inflicts tiny "microtears" in muscle fibers. The damaged area attracts the satellite cells, which incorporate themselves into the muscle tissue and begin producing proteins to fill the gap. Significantly, the number of nuclei passing from the satellite cells into the damaged area of the fiber is greater than the number of nuclei lost when the gap opened up. As a result, in that part of the fiber, more protein can be produced and supported. Gradually, as more microtears are repaired in this

Genetic vaccines now being developed to help the elderly increase their muscle mass will inevitably be abused by athletes and bodybuilders.

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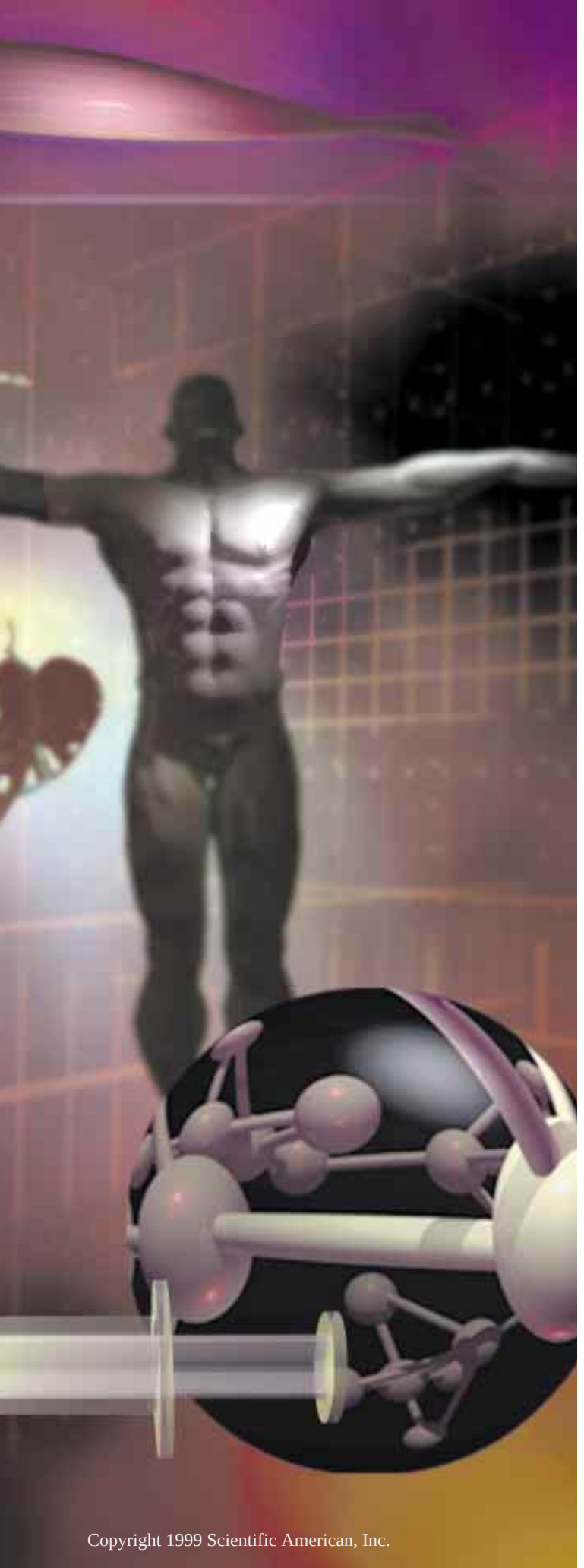

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manner, the overall number of nuclei grows, as does the fiber itself.

In order to produce a protein, a muscle cell—like any cell in the body—must have a "blueprint" to specify the order in which amino acids should be put together to make the protein—that is, which protein will be created. This blueprint is a gene in the cell's nucleus, and the process by which the information gets out of the nucleus into the cytoplasm, where the protein will be made, starts with transcription. It occurs in the nucleus when a gene's information (encoded in DNA) is copied into a molecule called messenger RNA. The mRNA then carries this information outside the nucleus to structures known as ribosomes, which assemble amino acids into the protein—myosin or actin, say—specified by that gene. This latter process is called translation.

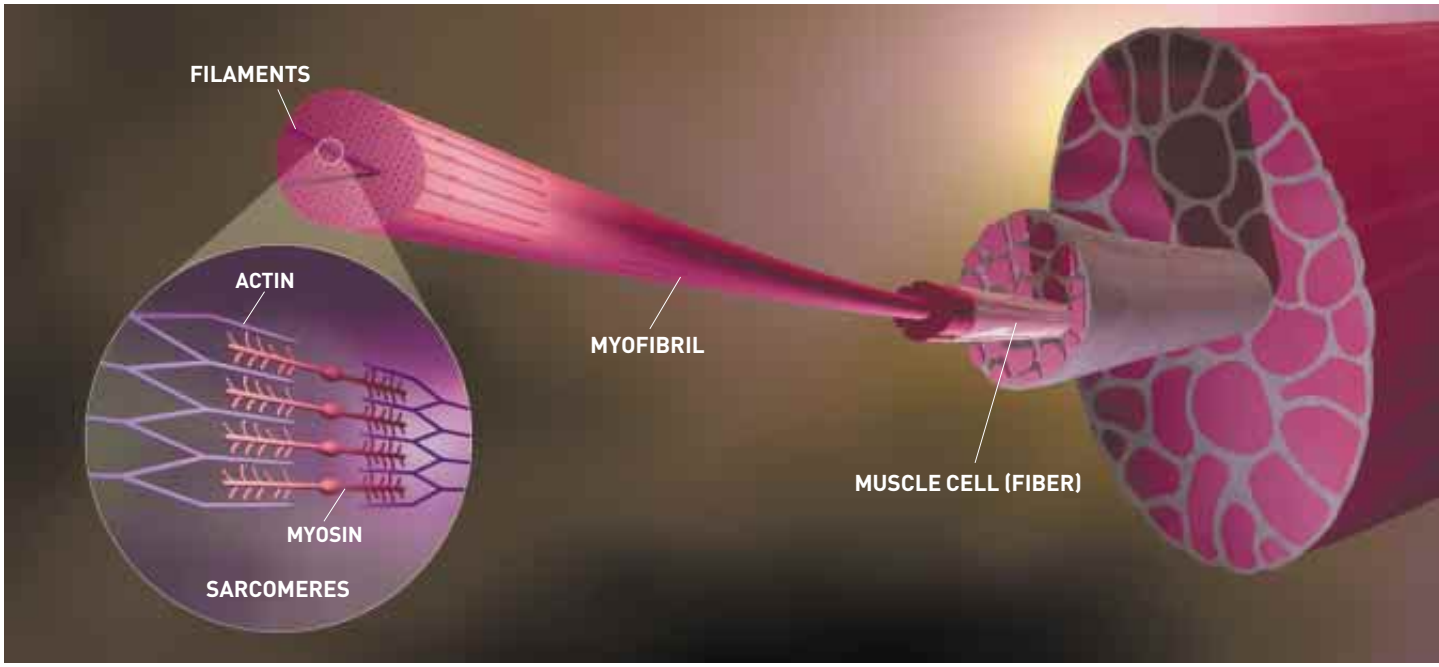
The source of biochemical complexity in muscle enlargement is not really transcription or translation but rather what precedes those processes: the many biochemical pathways that bring about transcription. Researchers know of dozens of different key biochemicals that initiate or sustain these pathways, and some suspect that there may actually be thousands. Most of these biochemicals are proteins that fall into five basic categories: sex hormones, like testosterone; thyroid hormones; insulinlike growth factors; fibroblast growth factor; and myriad other proteins lumped under the general term transcription factors. Some of these proteins are produced in organs such as the liver and circulate throughout the body; others are created locally, in specific muscle tissue, in response to exercise or stretching of that tissue.

These hormones, growth factors and transcription factors act in a variety of ways, often in conjunction with one another, to promote protein production. The many biochemical reactions are like a sprawling game with thousands of players, the goal being to get into the nucleus and, typically, to combine with a site on a chromosome known as a promoter region. This combination activates a nearby gene and triggers transcription.

As with any game, there are rules. Only the transcription factors, as their name implies, can get into the nucleus by themselves and activate genes. Hormones and growth factors spur transcription indirectly, usually in conjunction with transcription factors and other molecules called receptors. And one of the game's complexities is that sometimes transcription factors activate genes that produce more transcription factors.

As an example of how a hormone works, take testosterone. Produced by the testes and carried by the blood, it can penetrate a muscle cell's outer membrane and get into the cytoplasm. There it combines with a receptor floating free in the cytoplasm. The complex then enters the nucleus and binds to a promoter region to activate a gene and initiate transcription. Because anabolic steroids are merely synthetic versions of testosterone, this pathway is the one they trigger and exploit to build muscle.

Other pathways are even more complex. Some crucial ones begin with the binding of growth factors, for instance, to receptors that poke through the surface membranes of cells. When the parts outside the cell bind to a specific molecule, the union activates a series of chemical reactions inside the cell. For example, the binding of a growth factor to its receptor activates cascades of enzymes, called kinases, that modify other proteins in the cytoplasm, which in turn bind to promoter regions on chromosomes and otherwise regulate the activity of genes.



One of the most important growth factors is insulinlike growth factor-1 (IGF-1). During infancy and childhood, IGF-1 produced by the liver circulates throughout the body, rapidly expanding all the body's muscle fibers. The amount of this circulating, liver-produced IGF-1 eventually declines sharply, ending the early-life growth spurt. For muscle growth, the free ride is then over, and only exercise can add (and eventually, merely maintain) muscle mass. IGF-1 and other growth factors continue to play a major role, but they are released only locally in muscle during exercise or in response to injury.

Significantly, IGF-1 concentrations are high around the tiny tears in muscle fibers caused by exercise. Researchers believe that the growth factor plays a major role in attracting the satellite cells to the damaged area.

MIGHTY MICE

It was this local, muscle-specific form of IGF-1 that the University of Pennsylvania researchers exploited in their genetic experiments on mice. The Penn team, led by H. Lee Sweeney, took the gene that codes for the rodent form of muscle-specific IGF-1 and put it in a virus. Viruses can be useful for splicing engineered genes into cells because they target the nucleus, inserting the genes into a chromosome so that the DNA is not lost over time.

Besides the gene for IGF-1, the virus's DNA payload consists of other genetic material, such as a promoter region. Sweeney and his colleagues designed the promoter region so that it would always be "on," in effect inducing transcription of the *IGF-1* gene all the time.

Injected into a mouse's leg, the virus eventually got into 50 to 75 percent of the leg's muscle cells, Sweeney estimates. In each cell, the virus entered the cytoplasm and broke up, releasing the engineered gene and the associated genetic material. By mechanisms not well understood, the gene and other DNA became integrated into the nucleus's own DNA. Intriguingly, the invading DNA seemed to position itself randomly on a chromosome, Sweeney reports.

Once on the chromosome, with its promoter region stuck in the on position, the engineered gene started transcribing mRNA for muscle-specific IGF-1. The transcription continued until the animal died, of old age.

Sweeney has so far performed dozens of trials on both young and older mice. When injected at a young age, the mice grew to be adults with 15 to 20 percent more muscle mass in the treated area than they would have had otherwise. Injected at maturity, on the other hand, the animals did not gain muscle mass but—significantly—they did not lose much, either. By keeping what they had, the elderly mice had on average 27 percent more muscle mass than their untreated counterparts. In mid-June, Sweeney was exercising four dozen treated animals to see whether exercise added any effects to treatment.

The University College London experiments were broadly similar to those at Penn. In the British experiments, the muscle-enhancing substance the cells were tricked into producing was one that the lead researcher, Geoffrey Goldspink, dubbed mechano-growth factor (MGF). The genes for mechano-growth factor and IGF-1 are so similar that mechano-growth factor is considered a form (the technical term is "isoform") of IGF-1.

As a vehicle to deliver the engineered gene to the muscle cells, however, the British researchers chose not a virus but a plasmid, a circular piece of DNA. Although arguably safer than viruses, plasmids are much less efficient at getting into cells. Also, a plasmid does not insert itself into a chromosome, so it eventually stops prompting production of the protein.

Nevertheless, some of the injected plasmids do get into nuclei (again, through mechanisms not well understood). The plasmids,

Injected at a **young age**, the mice **grew** to have **15 to 20 percent more muscle.**

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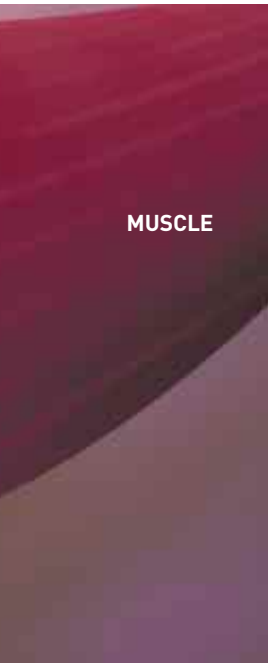

Muscle consists of cells full of strands called myofibrils, which are in turn made up of contractile units called sarcomeres. The key components of a sarcomere (*inset, exploded view*) are myosin (*red*) and actin (*lavender*). These protein molecules slide over one another as the sarcomere contracts and uncontracts. The myosin heads, which protrude outward from the filament's central stem, lock onto sites on the closest actin. The heads release one site and grip the next, "walking" the actin over the myosin.

too, had been given promoter regions stuck in the on position. So as soon as the plasmids got into muscle cell nuclei, they started cranking out mRNA for mechano-growth factor. Higher levels of MGF followed, and then an increase in muscle. According to Goldspink, injections into the legs of mice produced muscle mass increases of up to 20 percent—without exercise.

Weight lifters contemplating canceling their health-club memberships should read on. As it stands today, once a gene for a growth factor gets into a chromosome in a muscle cell nucleus, the cell continues churning out elevated quantities of the growth factor for as long as the animal lives.

"In principle the only thing lacking is a control mechanism to keep a hold on it," says Peter Schjerling, a research geneticist at the Copenhagen Muscle Research Center, which is affiliated with the University of Copenhagen and the city's University Hospital. "And there are a lot of people working on that," Schjerling adds.

The leading contender is known as a regulated promoter. It would be used in conjunction with a drug that turns the promoter region on and off. So long as the patient takes the drug, the promoter region of the engineered gene that has ensconced itself into the nucleus of some of his or her cells will be on, and the cells will produce the specified protein. When the patient stops taking the drug, the promoter region will switch off.

The problem is that many of the drugs for the experimental regulated promoters now available have toxic side effects. Still, Penn's Sweeney believes improvements are inevitable. "Better regulated promoters will come along," he asserts. "They are of too much interest to the biotechnology community. There are a lot of pharmaceutical companies working on them right now."

So far there have been no experiments with human subjects using the specific kind of virus (an adeno-associated virus) that Sweeney and colleagues are using. This situation is likely to change in the near future, however. A team led by James M. Wilson at the University of Pennsylvania has already used such a technique to produce in monkeys a protein called alpha sarcoglycan. Lack of the protein is a major factor in a type of muscular dystrophy that selectively affects the arms, legs and hips. The experiments with the monkeys have gone well, and within a year or two Wilson's team expects to begin trials of the treatment with humans afflicted with the disease, which is termed limb-girdle muscular dystrophy.

If that trial succeeds, Sweeney hopes to begin tests of his own, to produce muscle-specific IGF-1 in patients whose muscular dystrophy is so severe that they have no other recourse. If those trials go well, he will write a proposal to expand the experiments to include elderly people whose only health complaint is age-related muscle loss.

Not long after that, black-market versions of the genetic vaccines will inevitably begin flowing into the demimonde of bodybuilders, professional sports stars and international athletes, for whom even small increases in muscle can mean millions of dollars, greater prestige or both. "If in 20 years these viruses are available to treat muscular disease, they will be available to athletes seeking to gain a competitive edge," Sweeney notes. But, he continues, "it's not going to stop us from developing treatments for degenerative diseases."

GETTING PUMPED THE EASY WAY

It is easy to see how the narcissistic would find the drug irresistible. It would build muscle mainly where it was injected, making it possible for even the lazy and uncoordinated to sculpt their bodies by doing nothing more strenuous than lifting a hypodermic needle. Big biceps, nice calves and bulging pectorals will all be just a few injections away.

Of course, an instant physique of this kind will not come without a physiological price. To improve performance or look really buff, athletes and bodybuilders will probably need to take considerably larger doses than what doctors will prescribe for therapy. Thus, they would probably suffer some of the known or suspected side effects of abuse of IGF-1, such as an enlarged heart and, possibly, cardiac arrest. As with anabolic steroids, abuse of the genetic vaccine will most likely turn out to be more Faustian bargain than free ride.

Because the engineered genes would be copies of those that are normally in the nuclei of muscle cells, sports officials would find it extremely difficult to detect the abuse of a genetic vaccine—even if they were allowed to take a muscle biopsy. Today, however, biopsies are not permitted as part of a routine antidoping test. "Nor do I think athletes would be happy about submitting to a muscle biopsy just before a competitive event," Sweeney remarks.

From Samson's hair to Popeye's spinach, the idea of a strength-boosting talisman has long captivated us. Now, as science is poised to produce one, we might think about it in light of the varied motives that invariably accompany the application of any powerful new technology. It is hard to overstate the value of a genetic treatment that could let millions, perhaps billions, of people be more active, independent and resilient, improving their quality of life immeasurably. But it is anybody's guess what athletic competition will be like in an age of undetectable genetic enhancements.

"It could be like bodybuilding is today, where if you want to compete at the top level, you have no choice but to take anabolic steroids," says Garle, the antidoping expert.

Håkan Nyberg of the Swedish Sports Confederation is more optimistic. If in 15 or 20 years an age of genetically doped international superathletes arrives, he asks, "will sport keep its market value? I'm not sure. The driving force today is people like us who watch the competitions. Will we like watching a circus of artificial animals?"

ABOUT THE AUTHOR

GLENN ZORPETTE is co-editor of this issue of SCIENTIFIC AMERICAN PRESENTS. He donated muscle tissue from his thigh for use in some of the research described in this article.

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MAKING METHUSELAH

Immortality may not be in the cards, but worms, flies and pigeons may be able to teach us a thing or two about living better longer. **By Karen Hopkin**

"MOST PEOPLE are interested in living long and fruitful lives," begins the TV talk-show host, glancing at his notes.

"Fruit is good," interrupts the 2000-Year-Old Man. "Fruit kept me going for 140 years once when I was on a very strict diet. Mainly nectarines. I love that fruit. Half a peach, half a plum. It's a hell of a fruit."

In their classic 1950s comedy routine, Carl Reiner and Mel Brooks had at least part of it figured out: we all want to live long and fruitful lives. But the answer may not lie in nectarines.

It may lie in worms. Or, more specifically, in what scientists are learning about longevity as they study organisms as diverse as roundworms, fruit flies, monkeys and humans. Their findings lend hope to those who think we might someday be able to slow the process of human aging. "We can markedly increase the life span of simple organisms," reports Judith Campisi of Lawrence Berkeley National Laboratory. Researchers have found mutant worms, for example, that live up to 20 weeks—that's about eight times their normal life span and the equivalent of 600 years for you and me. They have also discovered treatments that can make normal human or animal cells grown in dishes live forever. And they have developed diet regimens that can increase life span while making animals healthier (though not necessarily happier).

"Saying that **in 20 years** we'll all **live to be 200** is utter **nonsense.**"

"We're undergoing a major scientific revolution in our understanding of aging," maintains Michael R. Rose of the University of California at Irvine. But will any of these developments translate into a sip from the fountain of youth? Will scientists ever come up with a simple pill that will keep you looking good and feeling fine into the triple digits? Or—gasp!—even forever?

Questions such as these capture the imagination—and spark heated debate. "Our studies suggest that the rate at which animals age is not fixed in stone or immutable," states Cynthia Kenyon of the University of California at San Francisco. Kenyon has identified mutations that vastly increase the life span of roundworms. "By changing a few genes," she continues, "we can outwit death and keep the worms alive and youthful much longer." Simply mutating genes that control the way these worms respond to hormones that resemble insulin, for instance, enables them to live two to five times longer. A treatment that produced similar results might work for people, too. "If we can make it to 90," she surmises, "I see no reason why, in principle, we couldn't make it to twice that."

Other scientists are less optimistic, though. "Such gene manipulations merely postpone the initiation of the aging process," declares U.C.S.F.'s Leonard Hayflick. "Aging is inevitable. Everything ages, including the universe." In 1961 Hayflick discovered that normal human cells, when grown in a culture dish, divide a limited number of times (about 50) and then die. This ultimate ceiling has been dubbed the Hayflick limit. "Saying that in 20 years we'll all live to be 200 is utter nonsense," Hayflick says.

THE TRIUMPH OF ENTROPY

First off, there's a difference between life span and life expectancy. Life expectancy, the number that appears on an insurance company actuarial table, reflects the average number of years a person can expect to live. Life span represents maximum longevity—the absolute number of years any human could hope to survive. The good news is that life expectancy has been on the rise for some time. People now live into their 70s, on average, which wasn't always the case. "99.99999 percent of the time humans have inhabited this planet, our life expectancy at birth has been no more than 18 to 20 years," Hayflick notes. The increase we enjoy now is largely the result of humankind having conquered many infectious diseases. What is more, studies show that we're living not only longer but healthier, according to Richard J. Hodes, director of the National Institutes of Health's National Institute on Aging. As a population, we are less plagued than ever before by physical infirmity, muscle wasting, osteoporosis and the like.

But how old can we possibly live to be? Tests of simple ani-

CYNTHIA TURNER

Is a fountain of youth in your future? By elucidating the factors that drive the aging process, researchers are hoping one day to postpone the inevitable ravages of age—and perhaps prolong life.

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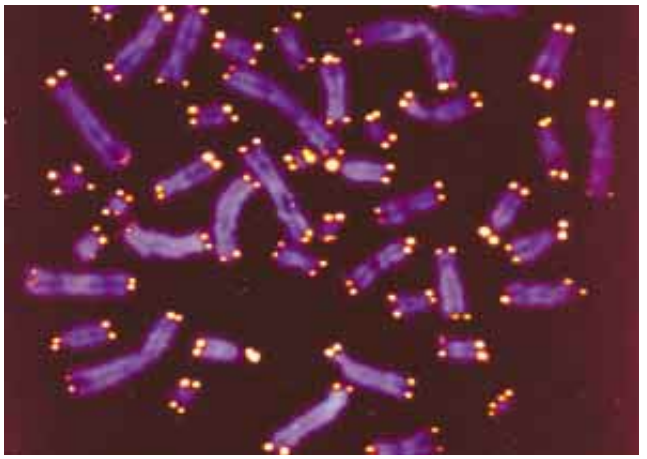

COURTESY OF GERON CORPORATION

Telomeres, which show up as glowing caps on the chromosomes above, may be the molecular timekeepers of the body. Each time a cell divides, they get a little shorter; at a crucial limit, the cell dies.

mals such as Kenyon's worms suggest there may be no upper limit, observes Rose, who studies aging in flies.

"It's hard to imagine, though, that we could live past 200," says Leonard P. Guarente of the Massachusetts Institute of Technology, who has correlated a mutation that accelerates aging in yeast with a premature aging syndrome in humans. "If we extend life span even a few years, cancer will kill everybody." And even if we duck cancer, he continues, wear and tear will weaken our veins and arteries, and our organs will eventually have to be patched up or replaced.

Even eliminating the diseases that now kill us would not increase our life expectancy substantially, Hayflick argues. Cure heart disease, add a dozen years; cancer, two or three more, he claims. "So if you cured both tomorrow morning, you'd only increase life expectancy by another 15 years. That's it, period. End of sentence." Hayflick believes that the human life span may be fixed by our genes at an upper limit of about 125 years.

Our maximum life span may have become set during evolution, because there is really no need for any creature to live beyond its reproductive years. Humans escape this seemingly cruel contract, generally speaking, because we have no natural predators hunting down the infirm or elderly members of our society. As far as evolution is concerned, by the time an animal bears children, it has fulfilled its biological destiny to pass on its genes and is just taking up space and sponging off its kids.

In any case, evolutionarily speaking, there must be a price to be paid for longevity, suggests Steven Austad of the University of Idaho, who studies aging in wild mice, opossums and birds. "Otherwise we'd all be long-lived."

But maybe we only make that argument because we're one of the longest-lived animals around, Kenyon counters. "If we were dogs, we'd look at humans and think, 'Hey, they live for a really long time, why can't we?' "

Even if natural selection did not favor the evolution of humans with the longest life spans, Hodes declares, "there's no reason why we can't change that." But to come up with potential therapies to slow or halt aging, we first need to understand why we age.

BEGINNING AT THE END

By now almost everyone has heard of telomeres—the bits of repetitive DNA sequences that cap and protect the ends of our chromosomes. Even the border guard who checked Kenyon's passport as she crossed into Canada to attend a recent conference on aging emitted a knowing "Ah, telomeres" when she described the purpose of her visit. But how do telomeres relate to aging?

There's no doubt that telomeres are important for keeping cells alive in culture dishes in a laboratory. Allow connective tissue cells called fibroblasts to grow in culture and their telomeres get shorter and shorter each time the cells divide. And when a cell's telomeres shorten enough, they signal the cell to stop dividing. Activate telomerase—an enzyme that rebuilds telomeres—and cultured cells become immortal. Cancer cells can keep dividing in part because they reactivate their telomerase.

But is telomere shortening involved in aging in the body? It's debatable. In the body, telomeres do dwindle in size as cells age, eventually shrinking to a length that would signal the same cells to stop dividing in a culture dish. But there's no direct evidence that human cells stop growing in the body because their telomeres are too short, Guarente points out. "Cells from old people grow just fine in culture," he says. And as far as we know, Austad adds, "animals don't typically die because their cells don't divide any longer."

Still, researchers who earn their living studying telomeres are hedging their bets. "It's simply too early to judge," asserts Titia de Lange of the Rockefeller University. "We just do not know enough about telomeres and aging in humans."

That's where the mice come in. To examine more directly the link between telomeres and aging, Ronald A. DePinho of the Dana-Farber Cancer Institute in Boston has generated mice that lack telomerase and found that as these animals age their telomeres shrink. They also go gray and lose their hair—a result that de Lange deems "remarkable." The rodents do not, however, develop many of the other maladies generally consid-

CYNTHIA KENYON, DELIA GARIGAN AND JAVIER APFELD
University of California, San Francisco

What a difference a gene makes. An elderly, two-week-old nematode worm (*left*) is sluggish and stiff compared with a two-day-old adult (*center*). In contrast, a mutant worm (*right*) lacking a gene that allows it to respond to hormonal signals continues to look youthful, even at two weeks.

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ered hallmarks of aging, such as cataracts, osteoporosis and cardiac disease. DePinho's conclusion: "Telomere shortening is not the cause of overall aging as we know it."

But certain cells or tissues—especially those that are dividing rapidly—probably do become crippled by shortened telomeres, suggests Calvin L. Harley of Geron Corporation in Menlo Park, Calif. Withered telomeres might help weaken the immune system, bones or skin, for example, all of which contain rapidly dividing cells and all of which are compromised as we age. In these cells, telomere shrinkage may reach a critical point, after which chromosomes begin to break. So someday doctors might boost immune function or strengthen bone or skin by turning on telomerase in the appropriate cells. Telomerase might also help extend the lives of the rapidly dividing endothelial cells that line blood vessels, allowing them to repair the wear and tear caused by a lifetime of vigorous blood flow.

Having long, luxuriant telomeres also seems to help animals deal with stress, DePinho posits. In his telomerase-deficient mice, old age and telomere loss act together to reduce the animals' ability to handle and survive stress, such as chemotherapy. Dwindling telomeres, he concludes, might explain why older people tend to have trouble recovering from surgery, infections or wounds. In the future, DePinho foresees, perhaps cancer patients scheduled for chemotherapy will also receive telomerase to prevent the treatment's side effects and enable their blood cells to survive and proliferate.

But would switching on telomerase all over the body allow people to live to the ripe old age of 150? "I doubt it," Harley declares. "When it comes to maximum human life span, so many other factors could be involved."

OXYGEN: A DEADLY GAS

Take free radicals, for example. Scientists have hypothesized since the 1950s that destructive molecules called free radicals might contribute to aging. These molecules—which are generated as byproducts of breaking down oxygen—can damage almost every critical component of cells, including DNA, proteins, and the fatty compounds that make up the inner and outer membranes of cells.

"Oxygen is toxic," declares Rajindar Sohal of Southern Methodist University. And the rate at which an animal ages may relate to how well it detoxifies oxygen radicals. Sohal finds that aged flies accumulate specific types of free-radical damage in their mitochondria—the tiny subcellular organelles that provide power to cells and tissues, including a fly's flight muscles. Martin Chalfie of Columbia University recently found that worms that lack a newly discovered form of an enzyme called catalase do not live as long as normal worms. Catalase disposes of hydrogen peroxide, a chemical that cells generate as they are converting oxygen into water. Further, Irvine's Rose has bred flies that live twice as long as normal. He finds that they show, among other things, an increase in the activity of superoxide dismutase (SOD)—an enzyme that destroys toxic oxygen radicals called superoxides.

Free radicals might also explain why pigeons live 35 years, 12 times longer than rats, animals that are about the same size. For the amount of oxygen they take in, pigeons produce fewer free radicals than rodents do. Perhaps we should be studying these animals to see how nature solves the aging problem, Austad suggests.

In the case of free radicals and aging, researchers need to be mindful of whether they are seeing cause and effect or simply a correlation, Guarente warns. Sure, oxygen radicals and cellular damage increase with age. But just because antioxidants increase life expectancy does not mean that free radicals cause aging. Banning motor vehicles would increase our life expectancy by about six months, Hayflick notes: "But that doesn't mean cars cause aging."

Free radicals can't be the bottom line when it comes to aging, Campisi agrees. "Mice and men live in the same toxic world."

So is SOD therapy likely in our future? "There's no guarantee it will work in humans," Rose admits. How about taking megadoses of antioxidants, such as vitamins C and E? That may not be good either, cautions Hodes, who recalls a study in which a group of smokers given the antioxidant beta carotene actually developed more cancers than a group of control subjects did.

NO SEX + LESS FOOD = LONG LIFE

Arguably the most striking results of studies examining ways to boost longevity come from investigations of the simplest organisms. Kenyon, for example, looks at worms that live two, three or four times longer than average. The creatures' longevity seems to boil down to the way they respond to hormones similar to insulin. Somehow mutations in this pathway allow these worms to stay frisky and svelte way past their prime, explains Kenyon, who adds, "I don't think, at the molecular level, we have much idea how."

Interestingly, she finds that removing the animals' sperm and egg cells does the same thing. Mature sex cells accelerate aging, perhaps by producing the insulinlike hormones that seem to control longevity in worms, Kenyon observes. Such an arrangement may allow animals that mature slowly to remain healthy long enough to reproduce.

This dovetails nicely with what Rose finds in his flies. He breeds longer-lived flies by delaying when the insects reproduce. "Like 'good' teenagers, they don't waste their energy on sex," he reports. As a result, they have more verve left for later. When these

RICHARD H. WEINDRUCH *University of Wisconsin*

Which of these mice is oldest? Actually, they're all the same age—39 months—which is beyond elderly in rodent-years. The two in the middle look sleek and healthy because they've been maintained on a diet containing half the calories eaten by their scraggly companions. Researchers are trying to find out how such calorie restriction can lead to long life.

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flies are 40 or 50 days old—over the hill in human terms—"they're flying around, fornicating and having a good time while the regular flies are dying," Rose says.

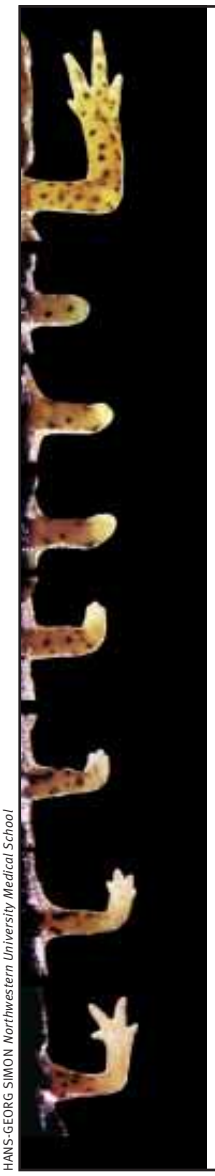
Does that mean people should put off having kids? "Oh, no, that's totally impractical," Rose responds. "What I'm doing to these flies is much more severe than what career women are doing." Besides, delaying parenthood would not affect your own life span—although it might help your descendants live it up 100 generations down the line.

The caveat? Scientists need to be certain that they are not looking at interventions that merely decrease metabolic rate, which also increases life span. Put a fly in the fridge, and it will live eight or nine times as long, Sohal states. But humans probably would not want to live longer if they had to chill out and hibernate. Although Rose's flies appear to have the same metabolic rate as adults, DePinho insists, "we need to bring these findings back to mammalian systems to see how relevant they are."

So far the only intervention that has been proved to slow aging in mammals is calorie restriction. Mice and rats raised on a diet high in nutrition but reduced in calories by 30 to 60 percent live about 30 percent longer—and by all accounts are healthier to boot, reports Richard H. Weindruch of the University of Wisconsin. In addition to his work with rodents, Weindruch has been following a colony of rhesus monkeys that have been on a restricted diet for 10 years. Compared with nondieting animals, these middle-aged monkeys have low insulin levels and are better able to regulate their glucose. They also have lower triglyceride levels, which means they are probably less prone to developing atherosclerosis, another benefit that might allow them to live longer.

The food-restricted monkeys also have less free-radical damage to their skeletal muscles than animals that are allowed to eat their fill. Together, these results suggest that the researchers who are finding that insulin regulation and oxygen radicals are important in aging in flies and worms are on to something.

But calorie restriction won't necessarily lead to another new "miracle" diet. "Nobody proposes that we starve people so they live to be 150," Campisi counters. And the truth is that this diet would not be easy for people to pull off, Weindruch admits. It's tricky to cut



HANS-GEORG SIMON *Northwestern University Medical School*

TALKIN' 'BOUT REGENERATION

FORGET THE fountain of youth. Slowing down aging may be less of a priority when we are able simply to replace faulty body parts as they wear out.

Okay, ordering Dad a new liver from Hammacher Schlemmer may not be in your immediate future. But right now biotech companies are placing stock in the idea that researchers and physicians may one day be able to direct the formation of spare body parts—be they bone, liver, pancreas or skin [see "Growing New Organs," on page 10].

To do that, scientists are taking tips from embryos. Cells and organs can be regrown, it stands to reason, with the same molecules that the embryo used to grow them in the first place. It is "unlocking the body's capacity to repair and regenerate," declares Doros Platika, president and CEO of Ontogeny in Cambridge, Mass.

Researchers at Ontogeny are treating animals with proteins with names as fanciful as Sonic hedgehog, Indian hedgehog and Patched—which all play an important role in the development of neurons, bone, cartilage, skin and hair—to stimulate the growth of the corresponding tissues in an adult. The dream is to get organs to regenerate in place inside the body, not implant a new part grown on the outside. "It may not be as sexy as a brain pulsing in a dish," Platika admits. But growing organs inside the body is better, he says, because it would allow molecular signals to be delivered in the correct context, directing organs to grow to the proper size and shape and to make the right connections with blood vessels, nerves and other tissues.

Cut off a newt's leg, and it grows back weeks later (and, in this sequence, in a lighter color). Why can't humans regenerate limbs and other body parts the same way? Enquiring scientists want to know.

"I don't think it's complete fantasy," comments Hans-Georg Simon, who studies regeneration in newts at Northwestern University Medical School. "The human body has quite remarkable capabilities for repair and regeneration." The problem is that we tend to lose that capacity as we age.

Very young children can regrow their fingertips—even up to the first knuckle, notes Clifford J. Tabin, a developmental biologist at Harvard Medical School. The trick is not rushing to heal the wound. Forming a scar is a quick and dirty way to prevent infection, but it eliminates the potential for growing new parts.

At least that's what happens in newts. Of course, these tiny creatures are at liberty to burrow into the muck for two months until they grow a new limb. Or pretty much a new anything, Tabin says. "Chop off any part of a newt, and if the animal survives, it'll grow back," he claims. It appears that adult newts retain something of the embryo's ability to allow all its cells to divide—something humans shut down, probably to avoid the runaway cell division that is characteristic of cancer.

In the next decades, regeneration might allow doctors to repair hearts, livers, skin and even injured spinal cords. But we might think twice about trying to regrow, say, a leg. "It took you 18 years to grow your leg to the size it is today," Tabin observes. "To wait 15 years to grow the right size leg is probably not as important as healing the wound to protect yourself from infection."

It's not a stretch to think that such techniques could be used to treat some of the disabilities associated with aging, according to Platika. Being able to regrow bone, for example, could save a woman with osteoporosis from getting a hip fracture that could keep her laid up in a nursing home instead of playing with her grandkids.

Ultimately, keeping people looking and feeling fit into their old age will be "more important than greatly extending life span," Platika asserts. "We want to be a bunch of gorgeous hunks and babes that are 100 years old." —*K.H.*

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that many calories and still maintain a nutritious diet. But if scientists can catalogue the physiological changes that occur in these animals, they may be able to design an intervention that accomplishes the same thing in humans who won't give up their Häagen-Dazs.

PILL ME

What does all this presage for potential antiaging therapies? The findings in calorie-restricted mammals suggest that to some degree longevity hinges on the hormones that control glucose metabolism, notes Richard A. Miller, a pathologist who studies aging mice at the University of Michigan School of Medicine. And the worm studies reveal that related hormonal pathways might regulate aging in all organisms. Animals that burn glucose more efficiently—extracting more energy from less blood sugar—somehow manage to live longer and healthier lives, Austad adds. This raises the possibility that therapies aimed at manipulating hormones might put the brakes on aging—or perhaps stave off aging-related ills such as osteoporosis, muscle loss, heart disease and cancer.

But even manipulating hormones may not be the whole answer. At the very least, we will need two different antiaging interventions, Guarente proposes: one for the brain and heart—cells that do not divide much—and another for cells that divide rapidly, such as skin. That is, unless you just want to look good. Adding telomerase might stretch the lives of skin cells, for example, but heart cells may need to be protected from the ravages of free radicals by somehow shoring up antioxidant defenses or regulating glucose metabolism.

"There's not going to be a magic bullet" to beat Father Time, Rose predicts. Campisi agrees. "To think that a single pill would slow all aging is extremely naive," she says. But someday certain interventions may be used to help particular systems of the body last longer and to prevent some age-related disorders. Retarding the death of neurons may not dramatically extend life span, for instance, but it might delay the onset of neurodegenerative diseases such as Alzheimer's disease so that they do not appear until age 90 or 100.

And as with anything, living longer may have its price. So-called dwarf mice, which are about one third the size of normal mice and live 50 to 70 percent longer, are sterile. Calorie restriction delays puberty in rats, mice and monkeys. And the maggots produced by long-lived flies die in greater numbers than those of normal flies do. "So we're never going to see childhood immunization against aging," Austad advises. But therapy later in life, after childbearing, might be an option.

Just beware the quick fix, Miller warns. Most of the people who will tell you that we can prolong the human life span are "quacks who have something to sell." If Austad were less scrupulous, he might be among them. "I like the royal jelly idea," he comments. People eat this gooey substance because bees feed it to their queens and queens live longer than drones, he says. "But mostly it's just bee poop." Perhaps the fact that researchers who study aging aren't getting rich hawking antiaging therapies suggests that they haven't found the answers—yet.

"Right now aging is still very much a black box," Guarente admits. "But we're standing on the brink of understanding." Chalfie predicts that "we'll learn a staggering amount about the biology of aging in the next 50 years. What we'll be able to do with that information, it's hard to say."

VONNEGUT'S VIEW OF AN AGELESS FUTURE

THE YEAR was 2158 A.D., and Lou and Emerald Schwartz were whispering on the balcony outside Lou's family's apartment on the seventy-sixth floor of Building 257 in Alden Village, a New York housing development that covered what had once been known as Southern Connecticut. Em and Lou weren't without their troubles, and they were out in the nippy air of the balcony because of them.

"Sometimes I get so mad, I feel like just up and diluting his anti-gerasone," said Em.

"That'd be against Nature, Em," said Lou, "it'd be murder. Besides, if he caught us tinkering with his anti-gerasone, not only would he disinherit us, he'd bust my neck. Just because he's one hundred and seventy-two doesn't mean Gramps isn't strong as a bull."

"Against Nature," said Em. "Who knows what Nature's like anymore? Ohhhhh—I don't guess I could ever bring myself to dilute his anti-gerasone or anything like that, but, gosh, Lou, a body can't help thinking Gramps is never going to leave if somebody doesn't help him along a little. Golly—we're so crowded a person can hardly turn around, and Verna's dying for a baby, and Melissa's gone thirty years without one."

"He's going to leave, Em. Just give him time.... He's talking about giving up anti-gerasone right after the five-hundred-mile Speedway Race."

"Yes—and before that it was the Olympics, and before that the World's Series, and before that the Presidential Elections, and before that I-don't-know-what. It's been just one excuse after another for fifty years now. I don't think we're ever going to get a room for ourselves or an egg or anything."

"All right—call me a failure!" said Lou. "What can I do? I work hard and make good money, but the whole thing, practically, is taxed away for defense and old age pensions."

Em put her arms around his neck. "Lou, hon, I'm not calling you a failure. You just haven't had a chance to be anything or have anything because Gramps and the rest of his generation won't leave and let somebody else take over."

"Yeah, yeah," said Lou gloomily. "You can't exactly blame 'em, though, can you? I mean, I wonder how quick we'll knock off the anti-gerasone when we get to Gramps' age."

"Sometimes I wish there wasn't any such thing as anti-gerasone!" said Emerald passionately. "Sometimes I wish folks just up and died regular as clockwork, without anything to say about it, instead of deciding themselves how long they're going to stay around. There ought to be a law against selling the stuff to anybody over one hundred and fifty."

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ABOUT THE AUTHOR

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ARE YOU READY FOR A NEW SENSATION?

As biology meets engineering, scientists are designing the sensory experiences of a new tomorrow. **By Kathryn S. Brown**

THE FLIMSY STRIP of golden film lying on John Wyatt's desk looks more like a candy wrapper than something you'd willingly put in your eye. Blow on it, and the 10-centimeter foil curls like cellophane. Rub it, and the shiny film squeaks faintly between your fingers. In fact, you have to peer rather closely to spot an unusual patchwork of squiggles: 100 electrodes, carefully arranged to jump-start cells in a damaged retina and, Wyatt hopes, allow the blind to see.

The film is part of a prototype retinal implant. For the past decade, Wyatt—an engineer at the Massachusetts Institute of Technology—and his colleagues have devoted a fifth-floor laboratory and countless hours to this tiny device. At first, even Wyatt doubted the project could succeed. The retina, he says, is more fragile than a wet Kleenex: it's a quarter of a millimeter thin and prone to tearing. In about 10 million Americans—those with disorders called retinitis pigmentosa and macular degeneration—the delicate rod and cone cells lining the retina's farthest edges die, although ganglion cells closer to the lens in the center survive. In 1988 Harvard Medical School neuro-ophthalmologist Joseph Rizzo asked Wyatt two key questions: Could scientists use electricity to jolt these leftover ganglion cells and force them to perceive images? Could they, in effect, engineer an electronic retina?

Try as he might, Wyatt couldn't think of a reason why the approach wouldn't work. Today Wyatt and Rizzo have tested their retinal implant on three patients. The most recent, a woman who participated in studies this spring, reported seeing a four-dot design that perfectly matched the electrode stimulation to her retina. "Those were our best results yet," Wyatt remarks.

Despite these early returns, however, a practical working implant is still years away. Wyatt likes to call the project a "classic case of science: 10 seconds of brilliance followed by 10 years of dogged work."

When it comes to improving our senses, researchers have some truly brilliant ideas. In the coming years, if lab bench dreams become reality, we will see even when our eyes are damaged, hear even when our ears grow old, smell a whole new repertoire of scents and taste a much sweeter world. True, the goals are high and the technical hurdles steep. But the basic science is coming together today, as the worlds of engineering and biology blend. "Really, we are limited [only] by our imagination," claims Richard J. H. Smith, a molecular geneticist at the University of Iowa.

Smith's imagination travels to the recesses of the inner ear and the pea-size cochlea that holds some 16,000 noise-detecting cells, each of which is equipped with several hairlike projections that have earned them the name "hair cells." This precious stock of cells is a gift at birth: they never multiply, but they do die. Loud noise, disease and just plain aging damage hair cells, muffling one's ability to hear sounds that once seemed crystal clear.

SENSING THE FUTURE

Today people with poor hearing have two choices: a cochlear implant or an old-fashioned hearing aid. A cochlear implant is a surgically implanted set of electrodes that stimulates inner-ear cells, whereas a hearing aid is essentially a removable microphone and receiver. But researchers say these technologies—which basically turn up life's volume—are like using a sledgehammer to set a watch. In the future, scientists hope to coax the inner ear gently into repairing itself—or, better yet, to protect hair cells from damage in the first place.

Regenerating damaged or destroyed hair cells has gone from a science-fiction dream to a realistic hope. "Fifteen years ago if I'd applied for a grant to study hair cell regeneration, I'd have been laughed out of town," says Edwin W Rubel of the University of Washington. "Now there are labs all over the world working on it."

One of the most promising approaches is to find genes that make hair cells grow and then pump them, via gene therapy, into a patient's ear. This may not be as hard as it sounds. Smith and other investigators have already discovered more than 25 specific gene sequences that are involved in hearing loss or deafness, and the search has just begun. By starting with easy-to-spot genetic mutations that cause extreme, inherited troubles, such as the pro-

NICOLE ROSENTHAL

The buzz of a bee, the stripes of a butterfly, the perfume of a rose, the taste of a berry. It's all in the senses, and scientists are now on to how they work.

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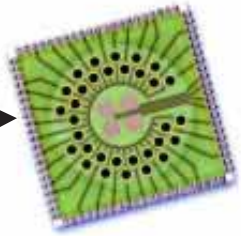
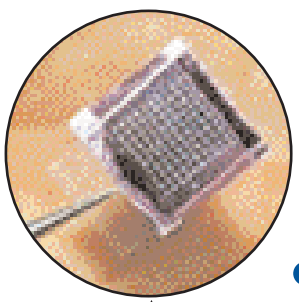
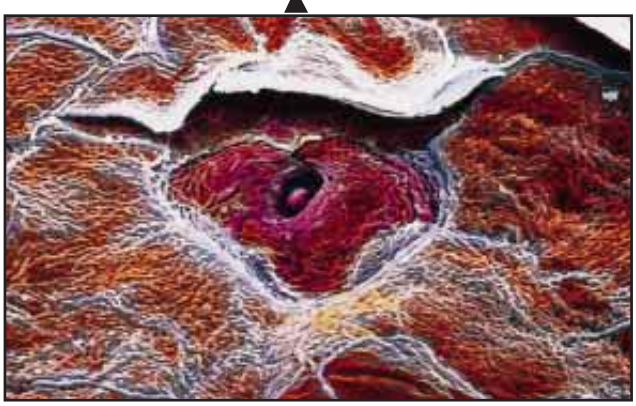


If someone tells you to wake up and smell the coffee, he or she might want you to use one of these. This orange blob is one of the thousands of olfactory receptors that make up the olfactory epithelium, a patch of mucous membrane way up in the nose that helps you sniff whether your milk has turned (among other things). Although the human nose isn't the best in the animal kingdom, researchers have mimicked it with a "nose on a chip" (*right*) that can be used by companies to monitor food quality. One day researchers might adapt the technology to develop an implant for people who have lost their sense of smell.





No, this isn't a close-up of one of those nubbly things on the surface of your tongue. Those are papillae; this is the opening of a taste bud. Hundreds of these barrel-shaped structures (*seen here from above*) are embedded in some types of papillae. When flavors enter the tiny pore in the center, they bind to and react with molecules called receptors on the surface of each of the taste cells, which make up the staves of the barrel. Scientists aren't producing an implantable artificial tongue just yet, but they have designed an electronic tongue, or e-tongue (*top*), that could be used to "taste" the quality of wine or the purity of water.

P. MOTTA *SPL/Photo Researchers, Inc.* (*top and bottom micrographs*); COURTESY OF CYRANO SCIENCES (*e-nose chip*); JOHN T. McDEVITT *University of Texas at Austin* (*e-tongue chip*)

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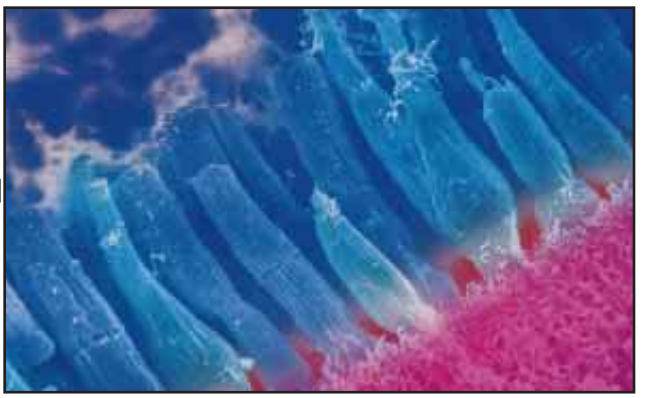
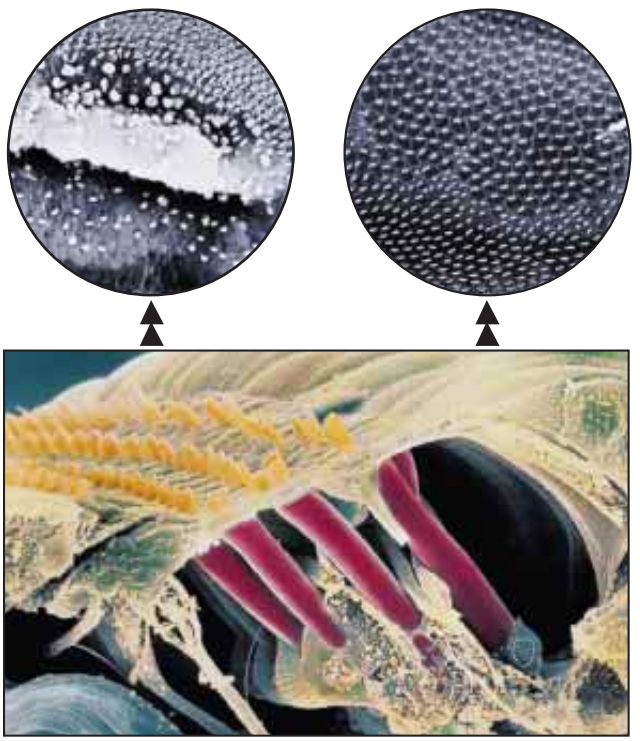


ZACH GOLD (*woman*); PHOTO RESEARCHERS, INC. (*top micrograph*); BETH PHILLIPS (*retinal implant*); SPL/PHOTO RESEARCHERS, INC. (*bottom micrograph*); JEFFREY T. CORWIN AND DOUGLAS A. COTANCHE *University of Virginia (hair cell micrographs)*

The rods and cones that make up the retina—the inside lining of the back of the eye—got their names for a reason that's obvious from this photograph. The rods are most important for black-and-white vision in dim light; the cones provide color vision and high visual acuity in bright light. But in people with diseases such as retinitis pigmentosa and macular degeneration, these sight cells start to die off, robbing the individuals of their vision. Bioengineers have now designed a retinal implant (*above left*) that could restore vision by allowing so-called ganglion cells, which are usually left intact in such diseases, to send electrical signals to the brain to register visual stimuli. The device is now being tested in people.



This detail from the cochlea, a tiny snail-shaped structure in the inner ear, reveals rows of sensory cells called hair cells. Each cell's minuscule projections register sounds and pass the information on to nerves that notify the brain. Exposure to loud noises and some drugs can destroy hair cells, causing hearing loss. Biologists are now trying to get damaged hair cells to regenerate. They've had some success with chicks: the electron micrographs above show hair cells disrupted by loud sounds (*left*) that have grown back 10 days later (*right*).

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We will **see** when our eyes are damaged, **hear** when our ears grow old, **taste** a much **sweeter world**.

gressive hearing loss that sometimes strikes college-age adults, researchers hope to find genes that might also cause more widespread, age-related hearing loss.

Other scientists are hunting for genes that are basic to hair cell development. In June geneticists at the Howard Hughes Medical Institute at Baylor College of Medicine, led by Huda Zoghbi, reported identifying a gene, named *Math1,* that is considered critical for the growth of hair cells in the inner ear. (*Math1* stands for m*ouse* at*onal* h*omolog-1*.) In their experiments, embryonic mice lacking *Math1* failed to develop hair cells at all. Adding extra copies of the human equivalent of *Math1* might trigger human hair cells to start growing again.

Once scientists know the correct genes to add, therapy becomes a matter of technique. Fortunately, Smith points out, the inner ear has two openings—the so-called round and oval windows—that doctors can use to shuttle genes into cells there. As with all gene therapy, scientists would have to find the right vectors—usually viruses engineered to carry an extra genetic payload—to get genes into specific cells. In some cases, physicians might bypass the faulty gene and instead simply repair the damage by, say, altering the chemical makeup of the fluid in the inner ear. "Depending on what we learn about hearing and genetics, we can come up with all kinds of creative ways to limit hearing loss or prevent it altogether," Smith predicts.

Some solutions might come from other animals. In 1974, during his first year of graduate school, Jeffrey T. Corwin, now a neuroscientist at the University of Virginia, discovered that sharks produce hundreds of thousands of hair cells throughout their lives. Corwin asked how—and whether human ears could be stimulated to do it, too. These questions still drive his research today.

Scientists now know that animals as diverse as zebrafish and chickens experience hair cell regeneration when their ears are damaged. By studying this faculty, investigators plan to pinpoint the key molecules involved, such as growth factors, and then design drugs based on the compounds. Even the runaway cell growth of cancer offers lessons in launching cell proliferation. If scientists learn how cancer nudges resting cells to suddenly start growing, they might also learn how to prompt hair cells to divide.

One day researchers could prevent hair cells from dying at all. With the right drug, predicts University of Virginia biomedical engineer Jonathan H. Spindel, it could be as simple as putting a few drops into someone's ear. Some studies suggest that nerve cells in the cochlea will grow toward certain growth factors. If that is true, a modified cochlear implant might slowly release growth factors into the ear, luring nerve cells to multiply toward stimulating electrodes that would keep them growing and healthy.

Peering into the future, in fact, investigators toy with the idea of dispensing with hair cells altogether and instead implanting an array of electrodes directly into the brain's crevices or onto its surface, where the electrodes would spark the perception of hearing. This approach, Corwin notes, is rife with questions—among them, exactly where to put the electrodes and how to avoid damaging the brain. But biocompatible materials and compact computers keep improving. At this rate, he forecasts, "areas of opportunity that once were the exclusive domain of science-fiction authors may come into areas of medical practice."

NICOLE ROSENTHAL

AN ARTIFICIAL NOSE?

For scientists who study smell, the world of nonfiction still holds many questions. Why can the scent of the family attic—or a stranger's perfume—prompt intense memories? How does your brain recognize a scent even before you can name it? And here's one that John S. Kauer really wants to answer: Why can't his wife smell the scent of the freesia flower?

Kauer, a neuroscientist at Tufts University, has been studying the olfactory system for 20 years, and he's still intrigued by anosmia, an absent or impaired sense of smell. Some people, like Kauer's wife, can't detect particular scents; others can barely smell anything at all. In fact, Kauer suggests, all human snouts could be missing out. "There is a world of [scent] molecules out there," he observes. "Just as there are animals that can see into the ultraviolet light or the infrared spectrum, there's likely a lot of odors we cannot smell."

Over the past few years Kauer and other scientists have been building "electronic noses": devices designed to sniff things we can't or might not want to, like land mines or spoiled food. Hewlett-Packard and Cyrano Sciences, a company based in Pasadena, Calif., for example, have designed an e-nose to help other companies monitor the quality of food and consumer products.

So far the e-noses only mimic human olfaction—and crudely at that, because each has just a few dozen sensors, compared with the millions of olfactory receptors in the human nose. But some scientists think that in the years to come, all this tinkering just might work in the other direction. "In a *Star Trek* kind of vision, you could imagine an artificial device that would allow you to recognize new scents in your environment," Kauer speculates. And just maybe, he posits, the device might live in a logical place: the lining of your own nose.

No matter how you engineer it, a stronger sniffer could improve life. Older adults whose sense of smell has gradually faded over the years often eat poorly, a reflection of the fact that most of food's flavor is really smell. According to the National Institute on Deafness and Other Communication Disorders in Bethesda, Md., more than 200,000 people in the U.S. visit a doctor for a smell or taste problem each year. And some of us might just want to enjoy the roses a bit more.

If Paul A. Grayson has his way, we'll soon get the chance. Grayson is president of an eclectic company called Ambryx in San Diego. Ambryx's goal is to turn today's molecular biology into a whole new field of products that pack a sensory punch. "What's

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missing from the 21st-century sensory experience?" Grayson asks. "The ability to enhance the sensory environment."

Run by a team of neuroscientists, corporate directors and even a cookbook author, Ambryx plans to bring sensory biochemistry to drug development and agricultural biotechnology, among other fields. One example might be perfume that's concocted according to a person's genetic profile. For example, a woman who can't smell musk—a common substance in perfumes—might prefer an undiluted jasmine scent. With DNA chip technology, companies could design a range of perfumes based on someone's unique olfactory receptor genes, says Peter Mombaerts, a neuroscientist at the Rockefeller University. This summer Ambryx announced a deal to use olfactory receptor genes discovered by Mombaerts's lab to look into such products.

YUMMY SCIENCE

It seems only natural, perhaps, that Ambryx also wants to dabble in taste. In February a team led by Nicholas J. P. Ryba of the National Institute of Dental and Craniofacial Research in Bethesda, Md., and Charles Zuker of the University of California at San Diego reported a molecular coup: the discovery of two sentinel-like molecules on the surface of the tongue's taste cells that sense sweet and bitter flavors. Within two months of the announcement, Ambryx had licensed rights to conduct studies of the receptors.

Researchers currently know little about the molecules, which were dubbed TR1 and TR2, but they could hold the key to a new wave of medications that lack a bitter taste or of foods with a special sweetness. Ryba and his colleagues are now inactivating the genes that encode the two receptors in mice that will then be tempted with a smorgasbord of sweet and bitter treats to help confirm the receptors' flavorful roles. He says his lab will next begin hunting for receptors that sense salty and sour flavors.

Our sense of taste endures lifelong, Ryba says, so high-tech tongue implants aren't likely in the near future. But at least one research group has engineered a new spin on taste: the electronic tongue. Like the e-nose, the e-tongue takes a cue from human biology, using chemical sensors as artificial taste buds to sample less than appealing—or downright dangerous—fluids, such as blood or urine.

Ever since chemist John T. McDevitt and his colleagues at the University of Texas at Austin created the e-tongue last year, they have been peppered with ideas for using the device as diverse as wine tasting and virus assays. A Japanese travel agency even called to ask whether McDevitt could design an e-tongue to test the water in a foreign country to determine if it is safe for travelers to drink.

Could all this lead full circle to offer new ways to manipulate human taste? "That's an important direction for the science that we'd like to explore in the future," McDevitt comments. "But at this point, I just don't know."

One thing is certain. No matter what the goal, every lab that is blending electronics and biology—whether it's in the ear, on the brain, inside the nose or lining the eye—must figure out how to make human and machine communicate. M.I.T.'s Wyatt quips that the retina, which is sensitive to even the slightest pressure, doesn't welcome a brick of a microchip any more than you'd like being caressed by a bulldozer. The challenge is to stimulate sensory areas such as the retina *gently*.

Wyatt and Rizzo's retinal implant would do just that. The film, which slips inside a tiny incision made in the retina during a surgical procedure, has three thin layers: a 12-photodiode array to perceive light changes; a gold-colored strip with 100 electrodes to fire up retinal cells; and a stimulator chip that helps to direct current to the electrodes.

In the future, a patient who has received an implant will wear special glasses equipped with a miniature camera that captures images. The glasses will sport a small laser that receives the camera's pictures and converts the visual information into electrical signals that travel to the implant. The implant, in turn, will activate the retina's ganglion cells to pick up the sensation of the image coming in and convey it to the brain, where it will be perceived as vision.

If it sounds complicated, Wyatt comments dryly, that's because it is. Nevertheless, he and his colleagues have been slowly perfecting the technique over a series of experiments—lengthening the duration of the current pulses and fine-tuning the microelectrode arrays. One looming question is how the retinal implant will work over time. So far the researchers have performed only afternoon-long experiments, after which the microelectric array is removed.

Since Wyatt and Rizzo's work began, two other groups in the U.S. have taken up the cause. One is Optobionics, a start-up company headed by Wheaton, Ill., ophthalmologist Alan Y. Chow. Optobionics is now testing its implant, which is named the artificial silicon retina, in rabbits. The Optobionics device is a subretinal implant, meaning it's surgically implanted beneath the retina. It is different from the M.I.T. group's retinal implant in that it connects to the back side—the photoreceptor side—of the retina rather than to ganglion cells. The second team, a group of scientists at Johns Hopkins University and at North Carolina State University, is pursuing a retinal implant similar to Wyatt and Rizzo's. The device is promising, although researchers must still demonstrate its long-term biocompatibility with the tissues of the eye, says Wentai Liu of N.C.S.U.

Although it is unusual today, an artificial retina could fit quite comfortably into the bionic body of tomorrow. Eventually, Liu predicts, investigators might create miniature computer chips that can be integrated fully into the body, allowing someone to recover from any injury with the help of internal electronic signals. "That's the next century," he says. "Right now we'll be very excited if we can just help people recover their sight."

"Areas of opportunity that once were the **exclusive domain** of science-fiction authors may come into areas of **medical practice."**

ABOUT THE AUTHOR

KATHRYN S. BROWN is a science writer based in Columbia, Mo. She would use an e-nose to stop and smell the roses (or lavender) and an e-tongue to savor even more dark chocolate.

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FEELING THE FUTURE

Our sense of touch will not only be replaceable, it will be enhanceable. **By Evelyn Strauss**

EVEN THE PHONE COMPANY has tried to exploit our need to touch. The old AT&T advertisements exhorted us to "Reach out. Reach out and touch someone." In the foreseeable future, this will become more than merely a metaphor. In the next several decades, some scientists predict they will be able to reconstitute the sense of touch in people who have lost limbs or sustained nerve damage and to extend the sensation into virtual worlds for the rest of us.

Imagine: A father who lost his arms uses a prosthetic hand to stroke his son's head. He relishes the familiar feel of the fine hair as he twirls a strand. After hearing about the day's water-gun battle and what the turtle ate for dinner, he kisses his child goodnight. Then he switches off his computer, and his son—who is a continent away—disappears.

This won't happen tomorrow. But scientists are already finding ways to rewire injured nervous systems, and they can already make three-dimensional objects that exist only inside computer software feel incredibly real.

Although spinal cord injuries derail communication between the brain and the muscles, the muscles can often still work if they are stimulated by some other means, such as a pulse of electricity. Researchers are taking advantage of this potential by building devices called neural prostheses that allow people to use motions that they can still command to perform various activities. A shrug of the shoulder, for example, can trigger a stimulator to send an electrical signal to the muscles that would make a missing hand grasp.

Right now the state-of-the-art device allows people to control up to 10 muscles, but researchers are striving to add more. "The next-generation system might supply the ability to hold an object above your head," suggests Jeanne O. Teeter of the Louis Stokes Cleveland Department of Veterans Affairs Medical Center. Bioengineers are already implanting parts of these mechanisms, and they envision a time when patients will carry entire systems under their skin that are capable of performing multiple functions.

And all may not be lost forever for people who have sustained serious injuries that leave them with virtually no voluntary muscle control. "We're looking to the brain to control neural prostheses," Teeter says. People can learn to make reproducible changes in brainwave patterns, she explains, and several research groups have already developed technology that allows people who are severely disabled to use this ability to move a cursor on a computer screen. Teeter would like to harness brain activity so disabled people could move their hands and legs "just by thinking about it."

Scientists might eventually improve on current nerve regeneration techniques to the point where they figure out how to use human nerves for the purpose instead of electrical wires. "Some people are trying to graft nerves around the area of injury to the peripheral nerves beyond," comments Joseph E. Kutz of the physicians' group Kleinert Kutz and Associates in Louisville, Ky. He emphasizes, however, that this approach is "still experimental. There's nothing yet that we're able to use in humans."

PHANTOM CONTROL

In contrast to people with spinal cord injuries, amputees retain uninterrupted nerve connections between the limb stump and their brain. Some people even feel as if their limbs are still there and maintain a sense of control over their missing parts. Such people typically can move muscles or ligaments that would otherwise operate missing fingers. This ability provides a critical link to restoring capacity. Engineers are devising systems that attempt to mimic a natural limb by hooking up muscles and nerves that once controlled some body part to a prosthetic version of it. William Craelius of Rutgers University is one of those engineers. He is developing a system with multiple, independently operating fingers—an improvement on current prostheses that just open and close a claw. With his new mechanism, users can operate a computer mouse or punch the keys on a keyboard.

Movement is one thing, but what's missing for many is the ability to feel. "It's very difficult to control paralyzed parts of your

MATT MAHURIN

The prosthetic limbs of tomorrow will be wired directly to the user's brain.

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body if you don't get sensory feedback," states Thomas Sinkjaer, director of the Center for Sensory Motor Interaction at Åalborg University in Denmark.

As an object begins to slip, for instance, people with intact nervous systems grip slightly harder, but just enough to stop the slippage. "If we want to restore good motor functions, we need to find ways to plug into the sensory system and feed back that information to the subject or to a computer," Sinkjaer asserts. In some situations, computers that respond in a simple way to specific signals are likely to substitute quite well for the normal situation. "If you touch something hot, you let go," explains Vincent R. Hentz, a hand surgeon at the Stanford University School of Medicine. "It's a reflex. The signal doesn't go through the brain."

Sinkjaer's group is developing a technique for putting electrodes around a sensory nerve that receives messages from special receptor cells in the hand. The electrodes record the impulses running along the nerve, and this electrical traffic correlates with how tightly the hand is holding an object. In its current form, the electrode feeds that information into a computer that "decides how to adjust the grasp accordingly" and then stimulates the correct muscles, Sinkjaer describes.

The first human subject is happy with the results. "Before, he had about 15 minutes to eat because after that he'd be so fatigued from gripping the fork too hard, he wouldn't be able to hold it any more," Sinkjaer recalls. "Now he should be able to talk to the person sitting next to him at a dinner party." Sinkjaer hopes eventually to improve the system so it can distinguish, as the brain can, exactly which of the thousands of receptors that feed into a given nerve fiber are firing. But before he and his colleagues accomplish that, scientists will need to develop electrodes that interface with the relevant neural pathways more selectively than they currently do.

Already researchers can send information back to a person as opposed to a computer. This approach might help paraplegics relearn to walk because it could abolish the need to use their hands to sense their weight distribution as they stand between parallel bars during physical therapy. Wiring sensory electrodes from the soles of the feet to gadgets that transmit an electrical signal to the shoulders, for example, can tell people when they are standing evenly on both feet: they would feel similar sensations in their right and left shoulders. Investigators developing prosthetics for amputees are using systems that are similar conceptually, adds Paul D. LaBarre, a mechanical engineer at Seattle Orthopedic Group in Poulsbo, Wash. His company is designing artificial feet that tell the user when his or her heel hits the ground, for example, by translating that force into a signal felt elsewhere on the body, such as on the calf.

In the most elegant schemes, sensors would send a signal to the same nerves that had once led to the missing appendage. Along these lines, researchers are building prostheses that connect directly to severed nerves using a specialized electrode that activates a small number of nerve fibers when implanted in the stump. "If we stimulate nerve fibers [that carry information about touch, pain and other sensations], we can make the person feel like they're sensing something on their thumb even though there's no thumb there," reports neuroscientist Kenneth W. Horch of the University of Utah.

He also hopes to make gizmos that run in the other direction—allowing a person to control the limb as well as experience the sensation of touch from it. But for this to work, the nerve fibers that control the particular faculties that the researchers are trying to restore must still maintain their connections to the spinal cord.

MATT MAHURIN

Future prosthetic limbs will not only look—and feel—extraordinarily real, they will also be equipped with the sense of touch.

Results so far have shown that the approach is feasible, Horch says, although the project is still in its preliminary stages. The researchers have electrically stimulated the nerve stump of amputees and shown that people can feel as if the missing appendage is being touched. "The nervous system is still intact enough for this to work," he observes. "Now we're ready to do long-term studies on patients and actually try it out."

ENTER LEE MAJORS

In the long run, scientists fantasize about making "a bionic limb that would replace all the sensations and abilities the limb had before it was amputated, with full feedback of both external and internal stimulation," LaBarre envisages. He points out that sensing physical contact is just one of the many types of information you receive from your limbs. "If you flex your elbow with your eyes closed, you know it. And if someone kicks your leg, you feel that, too," he says. "We'd like you to get all of that information from a bionic limb."

But that's just the beginning: LaBarre foresees temperature sensors. Although these are already available in a research setting, the current versions do not appeal to patients, he says, because they have lots of external electrodes and wires. Eventually, however, he expects them to be improved so that they can be incorporated seamlessly into prosthetic systems.

LaBarre even suggests it might be a good idea to include a sense of pain in bionic limbs so their users can keep them out of harm's way. The inability to feel discomfort can cause major problems for strictly biological limbs. Diabetes, for instance, often leaves hands and feet numb, for reasons that are still not exactly

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clear. "Diabetics can walk around all day with a pebble in their shoe and not know it," LaBarre says. "They end up with a debilitating sore on the bottom of their foot."

Experts working toward these goals caution that the technical and scientific challenges to restoring touch are huge. Building implantable touch sensors for people with spinal cord injuries, for example, presents tremendous difficulties. "Normal skin has thousands of receptors in its top two layers," states Clayton Van Doren, assistant professor of orthopedics at Case Western Reserve University. "We'll be lucky to put in one somewhere deeper in the tissue." Furthermore, such a sensor needs to be safe enough to be left in the body for months or years and robust enough to hold up that long. More important, Van Doren points out, "we don't understand the relationship between physical stimuli and perception. Because of that, it's difficult to know how to re-create the process in people who have lost some part of it."

While scientists are encountering considerable obstacles trying to reproduce relatively simple sensations, such as how tightly someone is holding an object, those who are studying more sophisticated tactile experiences face an even more formidable task. "When I grasp fabric, I can tell whether it feels like silk versus a coarse wool," observes Lynette Jones, a biomedical scientist at the Massachusetts Institute of Technology. Yet researchers are making significant progress toward this goal. "We've identified which receptors in the skin give information to the brain about fine features on a surface, but we don't know exactly how the brain processes that to perceive texture," says Mandayam Srinivasan, director of M.I.T.'s Touch Lab.

Remote medical technology is already helping patients. Companies such as Intuitive Surgical in Mountain View, Calif., and Computer Motion in Santa Barbara, Calif., have systems that enable physicians to perform heart bypass surgery during a minimally invasive procedure. Instead of sawing open the breastbone and prying the ribs apart, they send a camera and other instruments into the chest through small holes. Surgeons sit at a console and operate the tools while they watch what they are doing on a stereo display monitor. This approach enhances dexterity and reduces small tremors from shaking hands. "It scales down the motions so the surgeon can do really intricate work," says Kenneth Salisbury, a mechanical engineer at M.I.T.

Future generations of these machines might give surgeons the capability to feel more complex sensations so they can do things such as "figure out how tight they're pulling sutures when tying a knot," forecasts Paul Millman, a mechanical engineer at Computer Motion. He would also like to incorporate palpating technology. "It would be good if surgeons [at the console] could run their finger along arteries and find blockages, which feel tough," he says, or find "nice, healthy vessels, which are springy. If they could get the same information through these ports as they can now when they open up the chest, that would be great."

Perhaps the most demanding applications of artificial-touch technology would be virtual sex and remote sex. So far most of the problems investigators are attacking require only a subset of the components of touch. Mimicking a sexual encounter would combine everything—force feedback as well as tactile and thermal sensations, for instance—into one system. "Current haptic devices are not good enough for cybersex or virtual sex," Srinivasan concludes. "You can feel contours and [flexibility], but it's still probably very far from what people would want."

Perhaps the most **demanding** applications of **artificial-touch technology** would be virtual sex and **remote sex.**

Yet another thorny problem will be figuring out how to make artificial parts that can transmit the feel of subtle textures to multiple digits or a whole hand. The spatial and temporal information produced when a person touches surfaces is apparently very important for feeling textures, according to Susan J. Lederman, professor of psychology and computing and information science at Queens University in Kingston, Ontario. "When you've got only one point of contact, you don't get the same information as you do when you run your fingers over [something]," she says.

INTO THE VIRTUAL WORLD

Some of the largest strides in feeling texture and other sensations are being made by those who are developing so-called haptic devices that let people receive touch stimuli in a remote location or in virtual reality [see "Getting Real in Cyberspace," on page 48]. Robert D. Howe, a mechanical engineer in the division of engineering and applied sciences at Harvard University, is developing palpation technology that would, for example, permit surgeons to feel inside a patient's body through tiny holes.

Instead of a single probe, his device contains dozens of pins that transmit forces independently. "We're interested in what you would feel spread across your fingertip if you rubbed it across a surface," he says. Surgeons might snake such a device through a miniature cut in the chest wall to feel for lumpy lung tumors without having to make an incision large enough to fit a hand.

Touch technologists are reluctant to talk about the sexual uses of their inventions, in part because there are so many other applications in the areas of medicine, training, design and other traditionally wholesome realms. In principle, though, people could strap devices onto different parts of their bodies that could enable them to interact with a virtual person or with someone real who happens to be thousands of miles away. "The holy grail—not just for cybersex but for haptic interactions with virtual environments—is to wear something like a bodysuit that generates forces on you directed by a computer that mimic the real world," Srinivasan comments. "Right now using haptic technology is more like exploring the world by poking at it with a stick."

Is all of this fantastic? Yes, but it will happen. And when it does, maybe you'll hear about it from an advertisement for a porn Web site—via feel-mail, of course. How's that for keeping in touch?

ABOUT THE AUTHOR

EVELYN STRAUSS is a freelance science writer who lives in Santa Cruz, Calif. She will be the first on-line for feel-mail, as long as her correspondents promise to send only pleasant sensations.

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GETTING REAL IN CYBERSPACE

Virtual reality is not in suspended animation. Lately researchers have made impressive advances in conveying the senses of smell and touch. **By David Pescovitz**

STANDING IN A CINEMA in a form-fitting black bodysuit and oversize spectacles, you are feeling a little foolish. But then the "projectionist" flips a switch, and suddenly a riotously colorful, panoramic view of a massive garden nearly overwhelms you. Giant, exotic flowers sway slowly under a rainbow sky, and the scent of fresh sunflowers and soil fills the air. You feel something rubbing gently against your leg and look down to find a two-headed purple hare staring up at you. Leaning down, you stroke its soft fur before it hops ahead in surreal slow motion. Moments later the hare pauses in midhop, turns to face you and, in a language you've never heard before but somehow understand, beckons you to follow it into the foliage.

A dream? Afraid so. But eventually that level of immersion during a moviegoing experience could become reality. Or at least virtual reality.

Born out of graphical information display and flight simulation experiments in the 1960s, the term "virtual reality" was coined in 1986 by Jaron Lanier, the dreadlocked young computer scientist who became the poster boy for the technology. Before long the media, futurists and various pundits were hyping it as a revolution in simulation, communications and entertainment much more advanced than it really was. "Virtual reality won't merely replace TV, it will eat it alive," science-fiction legend Arthur C. Clarke predicted in those days.

And it still may, someday, according to the engineers and scientists who are now quietly inventing the future of the technology. Today's state-of-the-art in virtual-reality entertainment can be found at Disney's DisneyQuest interactive theme parks and at the Universal Studios theme park in Orlando, Fla. Inside DisneyQuest, visitors fly through an Arabian cityscape on Aladdin's Magic Carpet, propelled by powerful Silicon Graphics Onyx2 computers. At Universal Studios Islands of Adventure, the Adventures of Spiderman ride takes visitors in a bucking and rocking vehicle through a high-speed, sensory-overloading three-dimensional cartoon.

Like Spiderman, it's amazing. And riding the Magic Carpet is quite a trip. But both have nothing to do with approximating reality.

"If I want to present someone with a virtual world that's believable, the first arbitrarily hard problem is that the computer-generated characters have to behave in a believable way," says Randy Pausch, co-director of the Entertainment Technology Center at Carnegie Mellon University and a consultant on DisneyQuest. "Walking around in a virtual ghost-town is doable. But for the characters in the world to respond to me in a meaningful way, you have to solve the entire artificial-intelligence problem. It'll be a real long time before I can talk to Yoda."

Artificially intelligent actors aside, the line between the virtual and real worlds has been progressively, albeit slowly, blurring. Interactive, real-time, three-dimensional graphics become more lifelike with each new generation of microprocessor. For example, the nauseating, herky-jerky motion of 1992's Dactyl Nightmare, the first breed of virtual-reality arcade games, is no match for the breathtaking scenes in the games that can be played at home on Sony's forthcoming PlayStation 2 console.

In the meantime, researchers are making impressive progress on the visual and spatial aspects of the virtual-reality experience. They are also starting to devise ways of incorporating into it the two other senses that could realistically be conveyed: smell and touch.

SEEING IS BELIEVING

In research laboratories, at least, the techniques to display virtual reality and control our avatars in virtual worlds have surpassed the joystick and cumbersome head-mounted display. Take the Vir-

JAMES KIRKLAND

Patrons of an entertainment fantasy will not only see a two-headed purple hare, they will also be able to stroke the creature's fur and smell the flowers and earthy scents of an imaginary garden.

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Lasers in a head-mounted display will **project images** right onto the **retinas.**

tual Retinal Display, built by Microvision in Seattle, based on technology licensed from the University of Seattle Human Interface Technology Laboratory. Eliminating the middleman of a television screen, the device projects a color image right onto the retina using lasers. Once the size and power requirements of the laser components shrink, high-resolution, head-mounted displays won't be much more cumbersome than a pair of Ray-Bans.

"In a single-spectacle-type system, we'll provide a wide field-of-view stereoscopic display that also tracks the eyes as the image is being viewed, permitting us to alter the imagery based on the fixation point of the two eyes," says Microvision's principal scientist, Thomas M. Lippert.

Meanwhile scientists at the University of North Carolina at Chapel Hill have built a wide-area body tracker in an 8-by-5.5-meter (26-by-18-foot) space. As you walk around the room, optical sensors worn on your body provide a computer with your location relative to a series of infrared-light-emitting diodes mounted on the ceiling. Your motion inside the room is then mapped onto your computer-generated form in the virtual world. As Yogi Berra supposedly said, "Wherever you go, there you are."

So in the quest for the ultimate virtual-reality experience, where do we go from here?

Follow your nose. It always knows. That's the mantra of Myron Krueger, a virtual-reality pioneer whose Artificial Reality Corporation in Vernon, Conn., is one of the few facilities tackling this underrated but powerful element of human sensation.

M. J. SHARP

Like a sextant in cyberspace, the silver-and-transparent item on top of the wearer's head is a head-mounted tracking device that updates the head's position in relation to an array of infrared-light-emitting diodes in the ceiling. Updated 1,500 times a second, the positional data go into a virtual-reality scene generator, which computes a picture for the viewer to look at, based on where his or her head is at each instant. The tracking device was built by Gary Bishop and his colleagues at the University of North Carolina at Chapel Hill.

We don't have the sniffing power of a bloodhound, Krueger explains, but the human nose is capable of detecting odorants in up to one part per trillion concentration, depending on whether the smell is foul, fragrant or somewhere in between. And in many arenas, from food preparation to chemistry, odor is one of the most useful senses in the body's arsenal. Indeed, Krueger's research into olfactory virtual reality began with the long-promised notion of telepresence surgery, in which a physician miles away from the patient conducts an operation using remote-controlled robotic instruments and video cameras.

Supported by a grant from the Defense Advanced Research Projects Agency, Krueger is searching for ways to give surgeons the olfactory clues that occur when, for example, a bowel is perforated. And there isn't a stack of previous research he can stand on to see the answer. The only existing technology used for science, which has enabled psychologists to study the effects of odors on mood, employs passive evaporation. The most volatile components evaporate first, causing the smell's characteristics to change with time, much like the scent of a perfume changes during the course of the day. The system is problematic for anything beyond short-term laboratory use.

SAYONARA, SMELLY SENSORAMA

As far as olfactory entertainment goes, technology hasn't progressed much beyond the gimmicky Sensorama technology used in conjunction with a few limited-release, location-specific entertainment films starting in the 1960s. "Quite simply, olfactory displays are very easy to do badly," Krueger says.

To enjoy the Sensorama experience, the user sat on a motorcycle seat and watched a stereo film of a trip through New York City. Wind blew against the user's face, the handles vibrated, and big-city odors like bus exhaust and pizza added to the fun. But not only did the odor hit the player in one burst rather than gradually, each smell could not be removed before the next one was added, resulting in a malodorous mishmash at the end of the ride.

Krueger's current prototype resembles a headset microphone aimed at the nose. Ten odors are stored in liquid form in a pack worn on your back. The scents are generated by ultrasonic forced evaporation—the molecules of the liquid are literally shaken until they evaporate. The system is integrated into a wireless head-mounted display that tracks your motion and, via the computer, signals the olfactory display at the appropriate time. When you move your head, Krueger says, you can detect an odor with a lag of less than a tenth of a second.

"If the smell increases as I approach a graphic object, it not only makes the object seem a little more real, it also makes the action of moving my head and body more real," he says. "There's a synergy between the action and the odor."

Before Krueger's olfactory display system is ready for your local virtual-reality cineplex, more work will have to be done on the odors themselves. "The technology of odor simulation is very lim-

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VIRTUAL TECHNOLOGIES

The feel of an object that does not exist can be conjured up with a haptic device, such as Virtual Technologies's CyberGrasp. Sensors on the glove indicate where each finger is relative to the virtual object, and computer-controlled tendons exert the appropriate forces on the fingers and hand to simulate the object's shape and texture.

"In the case of a joystick, you're really limited to simulating the few real-world activities that require a joystick—flying a plane, for example," Kramer says. "We want to immerse the entire hand and body into the computer, so you really can reach out and touch someone."

CyberGrasp is an exoskeleton for the hand that enables users to hold computer-generated objects and feel their shape. Worn like a glove, CyberGrasp fits over the company's CyberGlove hand-tracking system, which computes the location of the user's fingers as they relate to the virtual object. A network of six computer-controlled tendons, much like those inside the human hand, prevents the user from closing his or her hand beyond the form of the virtual object being held, while also pushing appropriately on the pads of each fingertip and the palm.

Originally funded by the U.S. Navy, which needs haptic technologies for telerobotic applications such as hazardous-waste removal and telesurgery, the CyberGrasp is a giant leap.

Still, holding someone's hand in a virtual world isn't the same as hugging them. What is needed, clearly, is a haptic suit. The difficulty in designing one, Kramer explains, is covering the entire body with the tremendous number of actuators necessary to make the sensory feedback high-fidelity. One possibility is to etch the actuators in silicon. These so-called microelectromechanical systems (MEMS) are inexpensively batch-produced using processes similar to those by which microchips are manufactured. But even many thousands of MEMS pushing and pinching your skin could not give you the sensation of tumbling down a hill.

"A suit with an array of actuators doesn't give you ground-reference forces," Kramer says. "You could feel a wave rippling across your body, but it's not going to knock you off your feet. We need a big breakthrough."

One possibility Kramer mentions is that of electromagnetics. He envisions a virtual-reality-equipped room that, like an MRI machine, is actually a giant magnet. Clad in a haptic suit with magnetic properties, the wearer would be buffeted like a paper clip under a refrigerator magnet.

When electromagnetic push comes to shove, totally immersive virtual reality that engages all your senses is many years away. But advances in raw technology, along with a better understanding of human psychology, will someday enable us to truly play inside our own science fictions.

"Hollywood paves the path and shows us the direction people want us to go in," Kramer says. "And we're trying to make good on those predictions."

Clad in a **haptic suit,** future moviegoers might be **buffeted like paper clips** under a refrigerator **magnet.**

ited beyond flowers and fruit," Krueger says. "And it's nonexistent for things like diesel fuel, explosives, all those things you might want for an action-adventure game."

FIRST-PERSON FUTURE

"Reach-out-and-grab-it" movies may very well be in our entertainment future, adds James F. Kramer, CEO of Virtual Technologies in Palo Alto, Calif. "In the future, Hollywood movies will be directed from a first-person perspective, so you'll see and feel the same things the main character does," Kramer insists. "You'll don a force-feedback glove, and when the actor reaches out and touches an object, you'll feel it, too."

Virtual reality that feels real? An elusive goal, to say the least, but one that Kramer is already reaching for with his CyberGrasp haptic feedback interface.

Current haptic devices—ranging from Microsoft's SideWinder Force Feedback Pro joystick to SensAble Technologies's Phantom, which enables a user to feel the scrape of a carving tool on a virtual sculpture, for example—all chain the user to a small workspace. They are fine for computer-aided design or "Fighter Ace" games but are simply too restricting for the free-form nature of most virtual-reality entertainment applications.

ABOUT THE AUTHOR

DAVID PESCOVITZ (david@pesco.net) is a freelance writer living in Oakland, Calif., and co-author of *Reality Check* (HardWired, 1996). He hopes the future looks like a cross between *Blade Runner* and *The Jetsons*.

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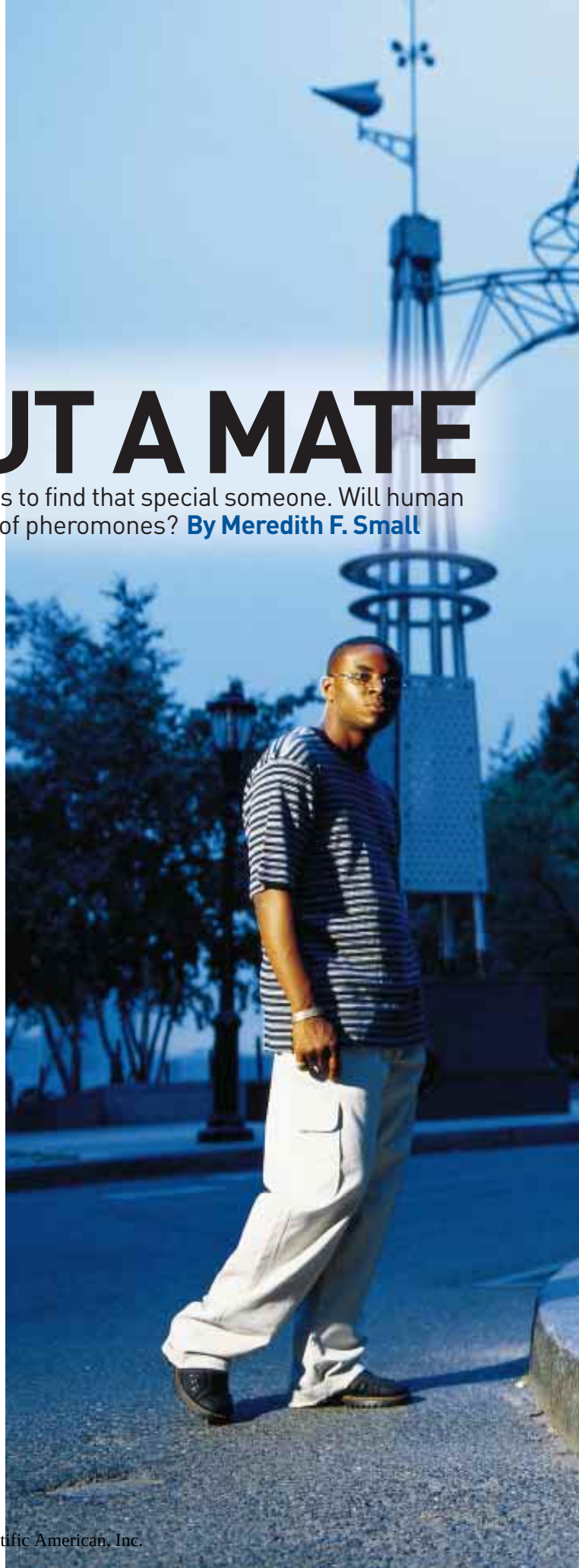
NOSING OUT A MATE

All other mammals rely on chemical attractants to find that special someone. Will human suitors of the future be able to pack the power of pheromones? **By Meredith F. Small**



PETER MURPHY

IT'S SATURDAY NIGHT in the year 2030 and time for your night on the town. It doesn't matter much what you wear, just be sure to dab on a little of that stuff you bought from the local pheromone shop. You might reach for a vial of your own essence that's been specially concentrated to make the most of your own attractive powers—or maybe you favor a synthesized version of the movie-star-of-the-moment's je ne sais quoi. Perhaps you go for a tube of the chemistry of some unknown person who just happens to be better-looking, more confident or blessed with superior genes to yours. Regardless, it's off to the neighborhood Fern-and-Sniff bar, and good luck!

Recent research suggests that humans, like many other organisms, can be sensitive to pheromones, which are thought to be odorless chemicals secreted from the body and picked up by a special organ in the nose. In the animal kingdom and among insects, pheromones convey information to other members of the species about an individual's gender, reproductive status and rank on the social ladder. Contrary to popular misunderstanding, pheromones are not strictly sex attractants, but they do play a role in the mating rituals of everything from moths to mice.

Do humans have pheromones? Right now the jury is still out. But scientists know that something—perhaps a pheromone—in the underarm sweat of some women can alter the menstrual cycles of other women who come in close contact with them. Some investigators even have early indications that such airborne chemicals might unconsciously influence who we choose as mates.

More than a few researchers predict that science will isolate an incontrovertible human pheromone early in the next century—in fact, some contend they already have. How will that change tomorrow's battle of the sexes? Will a chemical advantage in the mating dance be as close as the corner shop?

There is still debate over whether a human pheromone exists, but some scientists are out to isolate and bottle that "certain something" that seems to bring couples together.

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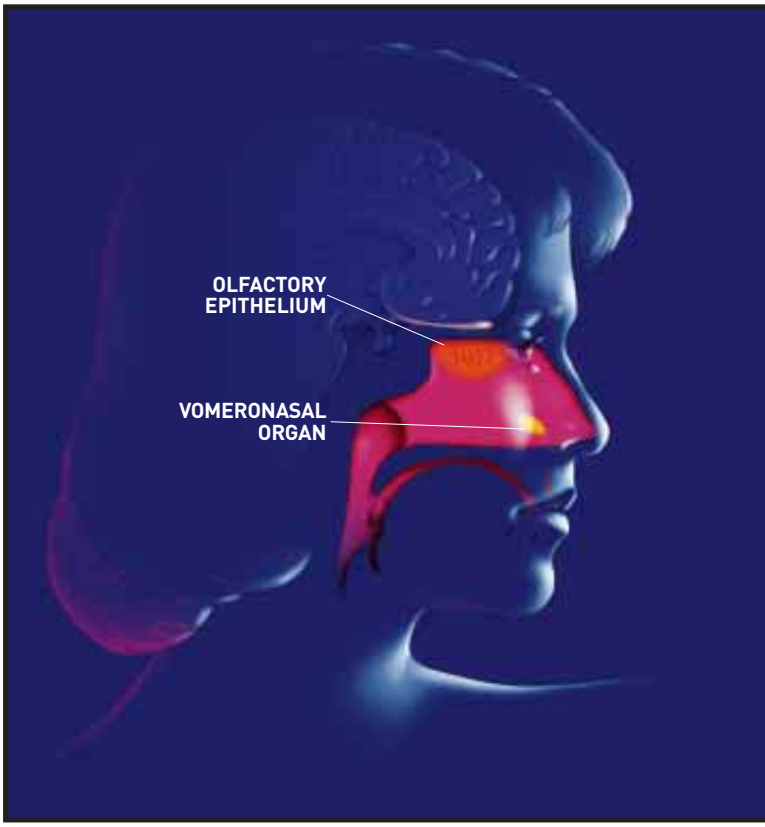
Other animals have been using their noses to find mates for a long time. Far up in the nasal passages of all mammals—including humans—are receptors that react to odors and pass on the signals we register as smells to the neocortex, the "gray matter" of the brain. But many claim we also possess another nasal sense called the vomeronasal organ (VNO), a pair of tiny sacs that lies closer to the nostrils. Receptor cells in the VNO supposedly pick up pheromones—which generally cannot be detected as a smell—and transmit the information to the hypothalamus and the limbic system, more primitive parts of the brain. These portions control the urges for such things as food and sex.

In the 1970s scientists showed that smell, whether of odors or pheromones, has a powerful role in mate choice—at least in rodents. Rodent urine, it seems, differs in odor and pheromone content according to what type of major histocompatibility complex (MHC) genes the animal has. MHC genes contain instructions for making the proteins that help an organism tell what belongs in its body and what is a potentially dangerous foreigner. Every rat or mouse (and, maybe, human) has its own chemical signature dictated by the MHC genes.

Interestingly, given their druthers, rodents sniff and then select mates with MHC genes that are quite different from their own. Such choices make good evolutionary sense: by choosing a mate whose MHC genes differ most markedly, rats and mice also have a good chance of mating with a partner whose other genes vary from theirs. Going for such variety could translate into offspring that are more equipped to fight off a range of infectious diseases.

If—and how—humans emit and track pheromones is not exactly clear. We belong to the order Primates, whose members are known for their well-developed senses of vision and touch. The trade-off for such visual and tactile acuity has supposedly been a less than keen sense of smell—a drawback that also seems to have blunted our pheromone-sensing abilities. In fact, most medical textbooks dismiss the human VNO as a vestigial structure that appears in the fetus and then nearly disappears later in development. But in the 1980s anatomists found evidence that the VNO exists in most adult people, even though it might not operate as well as it does in other mammals.



JOHN W. KARAPELOU

SOMETHING IN THE AIR

More recent behavioral studies, however, suggest that the human VNO functions just fine. Last year Martha K. McClintock and Kathleen Stern, scientists at the University of Chicago, showed that substances isolated from the sweat of women at various phases of the menstrual cycle can modulate the timing of ovulation in women with whom they associate.

McClintock first documented in the 1970s that the menstrual cycles of women who spend a lot of time together eventually synchronize, suggesting that something that can waft from one woman to another must be at work. Researchers then used cotton pads to see if they could swab the substance from female armpits. They first removed any odoriferous compounds from the pads and then wiped the remaining tasteless, odorless liquid onto the upper lips of other women. After a few months, they observed, the periods of the women who agreed to have the potential pheromone dabbed under their nose were in sync.

The same research protocol was used to show that men can influence the female cycle as well. A group of men offered up their armpit sweat, which was deodorized and then wiped on the upper lips of women with irregular menstrual cycles. Repeated exposure to the male secretions caused the women to cycle regularly, presumably by making them ovulate in a timely manner. Living with a man is presumed to have the same effect.

Although the studies substantiate the power of putative pheromones on female physiology, they say nothing about the role of the compounds in choosing a mate. For that, researchers have been turning to what might seem the least likely subjects—members of a closed religious sect in the Midwest that proscribes extramarital sex.

Carole Ober of the University of Chicago turned to the Hutterites, who routinely marry within their group, because she was intrigued by the rodent studies done in the 1970s. She wondered if humans, too, might subconsciously tend to mate with someone who has a differing MHC gene profile, which in humans is called the human leukocyte antigen (HLA) system.

Ober found that even though Hutterites as a group have very similar HLA profiles because of their history of intermarriage, the HLA genes of the wives she and her colleagues studied were quite different from those of their husbands. This suggested to Ober that the

More than a few **researchers predict** that science will **isolate** an incontrovertible **human pheromone** early in the next century.

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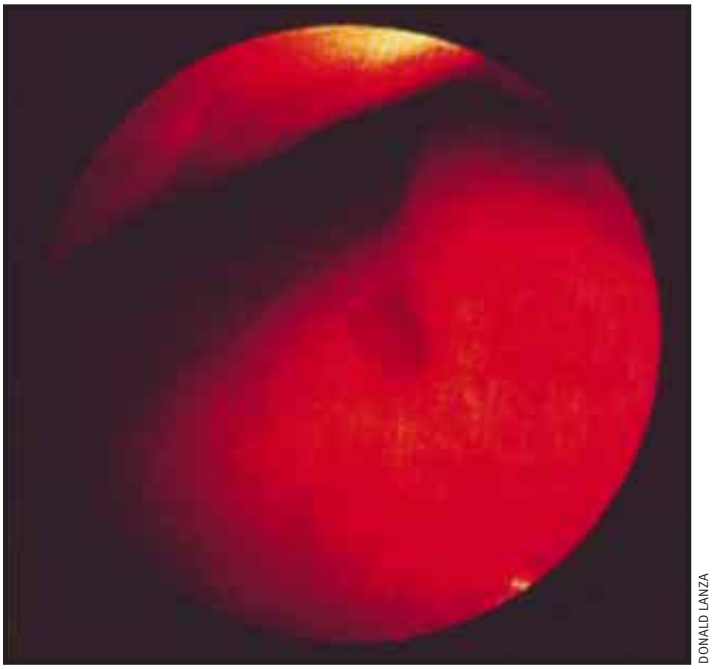

DONALD LANZA

It could be the last human organ to be identified by anatomists. The human vomeronasal organ (*close-up above*) consists of a pair of tiny, saclike structures that are thought to sense pheromones, which usually have no smell. The part of the nose that senses odors, the olfactory epithelium, lies higher up in the nasal cavity.

Hutterites were unwittingly optimizing the genetic diversity of their children by marrying partners whose genes were least like their own.

But how did the Hutterite couples choose partners with such different genes? Ober thinks the answer may lie in pheromones. Other studies have demonstrated that humans can smell the difference between mice with different MHC genes, she notes. So maybe the elusive chemistry that brings certain people together really is a pheromone. "I think this is likely," Ober says. "It would be odd if we could discriminate among the MHC types of another species but not among our own kind."

In 1995 evolutionary biologist Claus Wedekind of the University of Bern tested the possibility. He determined the HLA types of 49 women and 44 men (who were unknown to one another) and then asked each man to wear a cotton T-shirt for two consecutive nights. Next he asked the women, most of whom were ovulating and presumably at their most perceptive for choosing a mate, to sniff the shirts and record their reactions.

Wedekind reported that the women tended to prefer shirts worn by men with HLA types dissimilar from theirs. What is more, the shirts reminded them of current or former boyfriends. The women found T-shirts that had been worn by men with HLA types similar to their own unattractive and commented that they smelled like their fathers or brothers.

THAT COME-HITHER SMELL?

Did Wedekind's T-shirts contain human pheromones that either attracted or repelled the women? And, as many will want to know, how soon can the substance be bottled and sold?

Whether anyone has identified and purified an actual human pheromone is the subject of heated debate among people who know about the nose. For his part, David Berliner of Pherin in Menlo Park, Calif., claims that his company has produced two colognes based on human pheromones: one for men and one for women. But even Berliner isn't touting the potions as sex attractants. In fact, the men's cologne contains what he claims are male pheromones and the female scent, female essence. He says the colognes are intended to make the wearer relaxed and self-confident, which will draw in members of the opposite sex—a theory, by the way, that still hasn't been clinically tested. In any case, the current design might work just fine for gays and lesbians, and enterprising heterosexuals might try simply switching bottles.

Berliner isn't the only one purporting to sell human pheromones. Winifred B. Cutler of the Athena Institute for Women's Wellness Research has branched into commercial products as well. Her Chester Springs, Pa.–based company, which also conducts research, advertises vials of odorless synthetic human pheromones as additives to one's favorite scent. These scents are intended to "increase the romantic attention from the opposite sex," according to the ads.

Cutler asserts she has backed up this claim with a double-blind study of her men's solution. Men who used the compound in their aftershave lotion for six weeks reported that they increased the number of times they slept next to a woman and also said they had more sexual intercourse, she says. Because the men didn't masturbate more, she and her colleagues contend that the increase was not caused by heightened sex drive but by increased sex appeal.

What do other scientists think about all this? Even if Berliner and Cutler have isolated human pheromones—a point that is hotly contested—the stuff still might not matter when it comes to picking who to bed down with. "If we do find an effect of pheromones on mate choice," McClintock comments, "I believe the role will be modulatory, that is, in concert with existing mechanisms that are already rich, complicated and dependent on context."

Does this mean that if we can bottle our chemistry and dole it out in the future, the additive will change the way we fall in love? No, flowers and candlelight and sweet-nothings-in-the-ear will still be important, according to most accounts.

We are a behaviorally fickle species. When it comes to finding a mate, we are swayed by culture, pushed by family and locked into traditions. In many places across the globe, people even have their mates chosen for them, pheromones be damned. We also sidestep biology by washing off our body odors and any pheromones or diluting them with soap and perfume.

Perhaps in the future we will be able to better control the messy process of the mating dance with a touch of something that makes us especially appealing to others. That way we could concentrate on projecting the good points about our genetic constitutions and ensure the most biologically appropriate mate. Or more likely, being the smart and adventurous species that we are, we'll experiment with nature and splash on a dab of someone different each night—and find out exactly what the nose knows.

ABOUT THE AUTHOR

MEREDITH F. SMALL, professor of anthropology at Cornell University, writes frequently about science. She says this is one of her weirdest assignments ever.

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THE COMING MERGING OF MIND AND MACHINE

The accelerating pace of technological progress means that our intelligent creations will soon eclipse us—and that their creations will eventually eclipse them. **By Ray Kurzweil**

SOMETIME EARLY in the next century, the intelligence of machines will exceed that of humans. Within several decades, machines will exhibit the full range of human intellect, emotions and skills, ranging from musical and other creative aptitudes to physical movement. They will claim to have feelings and, unlike today's virtual personalities, will be very convincing when they tell us so. By 2019 a $1,000 computer will at least match the processing power of the human brain. By 2029 the software for intelligence will have been largely mastered, and the average personal computer will be equivalent to 1,000 brains.

Once computers achieve a level of intelligence comparable to that of humans, they will necessarily soar past it. For example, if I learn French, I can't readily download that learning to you. The reason is that for us, learning involves successions of stunningly complex patterns of interconnections among brain cells (neurons) and among the concentrations of biochemicals, known as neurotransmitters, that enable impulses to travel from neuron to neuron. We have no way of quickly downloading these patterns. But quick downloading will allow our nonbiological creations to share immediately what they learn with billions of other machines. Ultimately, nonbiological entities will master not only the sum total of their own knowledge but all of ours as well.

As this happens, there will no longer be a clear distinction between human and machine. We are already putting computers—neural implants—directly into people's brains to counteract Parkinson's disease and tremors from multiple sclerosis. We have cochlear implants that restore hearing. A retinal implant is being developed in the U.S. that is intended to provide at least some visual perception for some blind individuals, basically by replacing

EDMOND ALEXANDER

Within three decades, the author maintains, neural implants will be available that interface directly to our brain cells. The implants would enhance sensory experiences and improve our memory and thinking.

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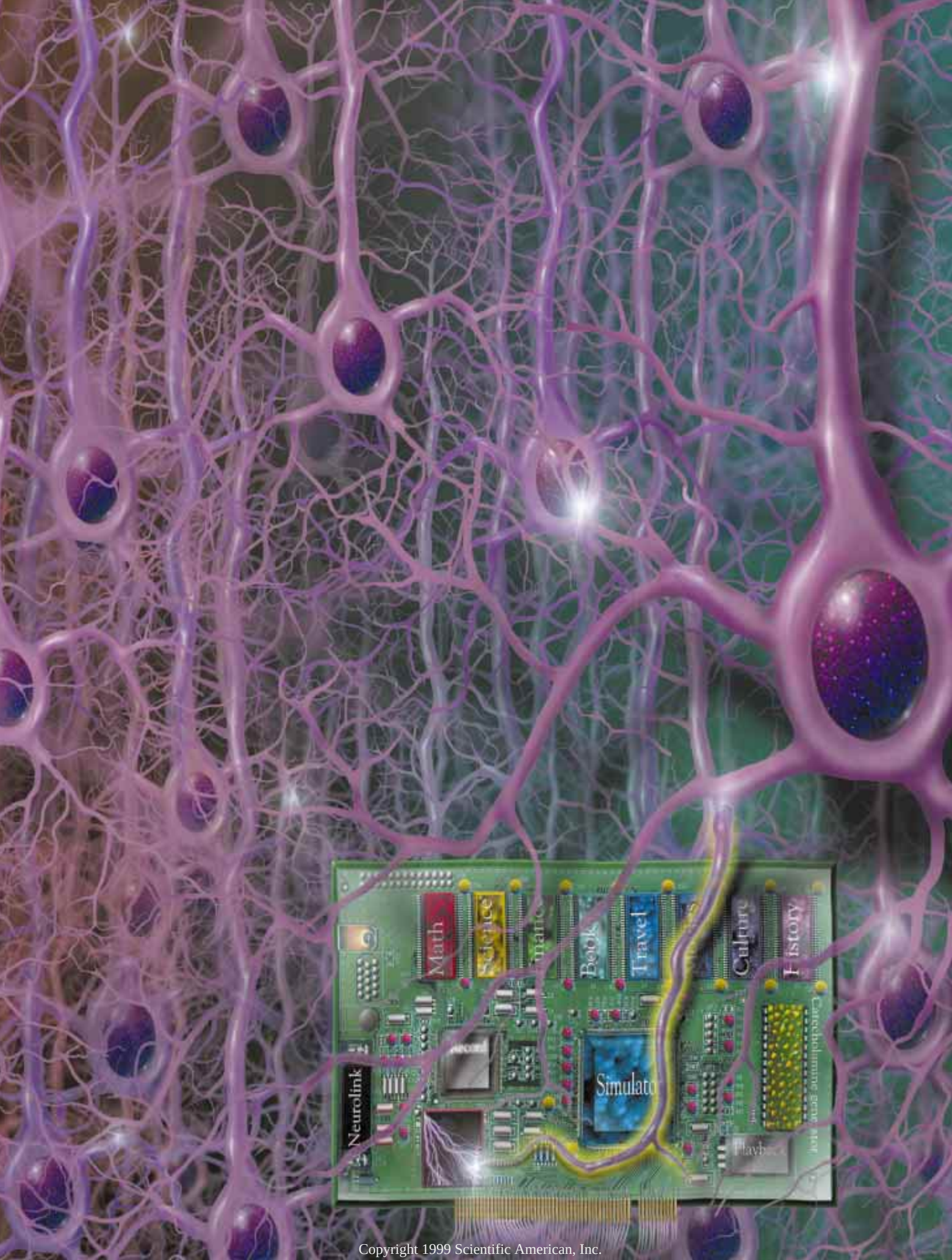

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certain visual-processing circuits of the brain. Recently scientists from Emory University implanted a chip in the brain of a paralyzed stroke victim that allows him to use his brainpower to move a cursor across a computer screen.

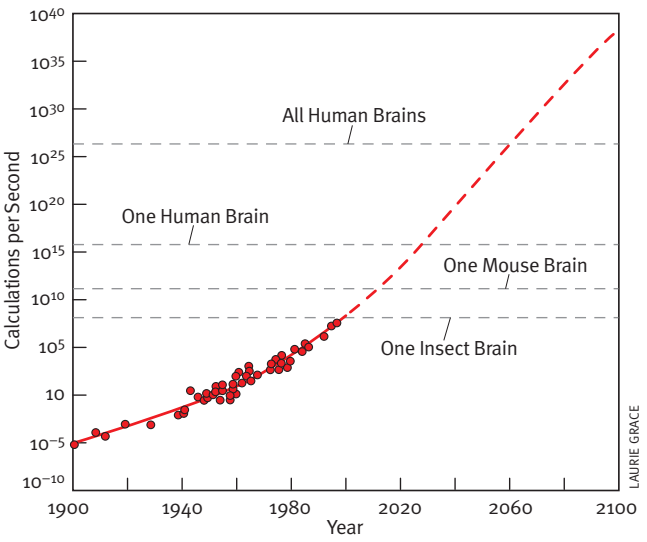
In the 2020s neural implants will improve our sensory experiences, memory and thinking. By 2030, instead of just phoning a friend, you will be able to meet in, say, a virtual Mozambican game preserve that will seem compellingly real. You will be able to have any type of experience—business, social, sexual—with anyone, real or simulated, regardless of physical proximity.

HOW LIFE AND TECHNOLOGY EVOLVE

To gain insight into the kinds of forecasts I have just made, it is important to recognize that technology is advancing exponentially. An exponential process starts slowly, but eventually its pace increases extremely rapidly. (A fuller documentation of my argument is contained in my new book, *The Age of Spiritual Machines*.)

The evolution of biological life and the evolution of technology have both followed the same pattern: they take a long time to get going, but advances build on one another and progress erupts at an increasingly furious pace. We are entering that explosive part of the technological evolution curve right now.

Consider: It took billions of years for Earth to form. It took two billion more for life to begin and almost as long for molecules to organize into the first multicellular plants and animals about 700 million years ago. The pace of evolution quickened as mammals inherited Earth some 65 million years ago. With the emergence of primates, evolutionary progress was measured in mere millions of years, leading to *Homo sapiens* perhaps 500,000 years ago.



The accelerating rate of progress in computing is demonstrated by this graph, which shows the amount of computing speed that $1,000 (in constant dollars) would buy, plotted as a function of time. Computer power per unit cost is now doubling every year.

The evolution of technology has been a continuation of the evolutionary process that gave rise to us—the technology-creating species—in the first place. It took tens of thousands of years for our ancestors to figure out that sharpening both sides of a stone created useful tools. Then, earlier in this millennium, the time required for a major paradigm shift in technology had shrunk to hundreds of years.

The pace continued to accelerate during the 19th century, during which technological progress was equal to that of the 10 centuries that came before it. Advancement in the first two decades of the 20th century matched that of the entire 19th century. Today significant technological transformations take just a few years; for example, the World Wide Web, already a ubiquitous form of communication and commerce, did not exist just nine years ago.

Computing technology is experiencing the same exponential growth. Over the past several decades, a key factor in this expansion has been described by Moore's Law. Gordon Moore, a co-founder of Intel, noted in the mid-1960s that technologists had been doubling the density of transistors on integrated circuits every 12 months. This meant computers were periodically doubling both in capacity and in speed per unit cost. In the mid-1970s Moore revised his observation of the doubling time to a more accurate estimate of about 24 months, and that trend has persisted through the 1990s.

After decades of devoted service, Moore's Law will have run its course around 2019. By that time, transistor features will be just a few atoms in width. But new computer architectures will continue the exponential growth of computing. For example, computing cubes are already being designed that will provide thousands of layers of circuits, not just one as in today's computer chips. Other technologies that promise orders-of-magnitude increases in computing density include nanotube circuits built from carbon atoms, optical computing, crystalline computing and molecular computing.

We can readily see the march of computing by plotting the speed (in instructions per second) per $1,000 (in constant dollars) of 49 famous calculating machines spanning the 20th century [*see illustration at left*]. The graph is a study in exponential growth: computer speed per unit cost doubled every three years between 1910 and 1950 and every two years between 1950 and 1966 and is now doubling every year. It took 90 years to achieve the first $1,000 computer capable of executing one million instructions per second (MIPS). Now we add an additional MIPS to a $1,000 computer every day.

WHY RETURNS ACCELERATE

Why do we see exponential progress occurring in biological life, technology and computing? It is the result of a fundamental attribute of any evolutionary process, a phenomenon I call the Law of Accelerating Returns. As order exponentially increases (which reflects the essence of evolution), the time between salient events grows shorter. Advancement speeds up. The returns—the valuable products of the process—accelerate at a nonlinear rate. The escalating growth in the price performance of computing is one important example of such accelerating returns.

A frequent criticism of predictions is that they rely on an unjustified extrapolation of current trends, without considering the forces that may alter those trends. But an evolutionary process accelerates because it builds on past achievements, including improvements in its own means for further evolution. The resources it needs to continue exponential growth are its own increasing order and the chaos in the environment in which the evolutionary process takes place, which provides the options for further diversity. These two resources are essentially without limit.

The Law of Accelerating Returns shows that by 2019 a $1,000 personal computer will have the processing power of the human

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brain—20 million billion calculations per second. Neuroscientists came up with this figure by taking an estimation of the number of neurons in the brain, 100 billion, and multiplying it by 1,000 connections per neuron and 200 calculations per second per connection. By 2055, $1,000 worth of computing will equal the processing power of all human brains on Earth (of course, I may be off by a year or two).

PROGRAMMING INTELLIGENCE

That's the prediction for processing power, which is a necessary but not sufficient condition for achieving human-level intelligence in machines. Of greater importance is the software of intelligence.

One approach to creating this software is to painstakingly program the rules of complex processes. We are getting good at this task in certain cases; the CYC (as in "encyclopedia") system designed by Douglas B. Lenat of Cycorp has more than one million rules that describe the intricacies of human common sense, and it is being applied to Internet search engines so that they return smarter answers to our queries.

Another approach is "complexity theory" (also known as chaos theory) computing, in which self-organizing algorithms gradually learn patterns of information in a manner analogous to human learning. One such method, neural nets, is based on simplified mathematical models of mammalian neurons. Another method, called genetic (or evolutionary) algorithms, is based on allowing intelligent solutions to develop gradually in a simulated process of evolution.

FANTASTIC VOYAGE

Although sophisticated robots that small are still several decades away at least, their utility for probing the innermost recesses of our bodies would be far-reaching. They would communicate wirelessly with one another and report their findings to other computers. The result would be a noninvasive scan of the brain taken from within.

Most of the technologies required for this scenario already exist, though not in the microscopic size required. Miniaturizing them to the tiny sizes needed, however, would reflect the essence of the Law of Accelerating Returns. For example, the translators on an integrated circuit have been shrinking by a factor of approximately 5.6 in each linear dimension every 10 years.

The capabilities of these embedded nanobots would not be limited to passive roles such as monitoring. Eventually they could be built to communicate directly with the neuronal circuits in our brains, enhancing or extending our mental capabilities. We already have electronic devices that can communicate with neurons by detecting their activity and either triggering nearby neurons to fire or suppressing them from firing. The embedded nanobots will be capable of reprogramming neural connections to provide virtual-reality experiences and to enhance our pattern recognition and other cognitive faculties.

To decode and understand the brain's information-processing methods (which, incidentally, combine both digital and analog methods), it is not necessary to see every connection, because there is a great deal of redundancy within each region. We are already applying insights from early stages of this reverse-engineering process. For example, in speech recognition, we have already decoded and copied the brain's early stages of sound processing.

If we **download** someone's **"mind file"** into a suitable medium, will the **entity** that emerges **be conscious?**

Ultimately, however, we will learn to program intelligence by copying the best intelligent entity we can get our hands on: the human brain itself. We will reverse-engineer the human brain, and fortunately for us it's not even copyrighted!

The most immediate way to reach this goal is by destructive scanning: take a brain frozen just before it was about to expire and examine one very thin slice at a time to reveal every neuron, interneuronal connection and concentration of neurotransmitters across each gap between neurons (these gaps are called synapses). One condemned killer has already allowed his brain and body to be scanned, and all 15 billion bytes of him can be accessed on the National Library of Medicine's Web site (www.nlm.nih.gov/research/visible/visible_gallery.html). The resolution of these scans is not nearly high enough for our purposes, but the data at least enable us to start thinking about these issues.

We also have noninvasive scanning techniques, including high-resolution magnetic resonance imaging (MRI) and others. Their increasing resolution and speed will eventually enable us to resolve the connections between neurons. The rapid improvement is again a result of the Law of Accelerating Returns, because massive computation is the main element in higher-resolution imaging.

Another approach would be to send microscopic robots (or "nanobots") into the bloodstream and program them to explore every capillary, monitoring the brain's connections and neurotransmitter concentrations.

Perhaps more interesting than this scanning-the-brain-to-understand-it approach would be scanning the brain for the purpose of downloading it. We would map the locations, interconnections, and contents of all the neurons, synapses and neurotransmitter concentrations. The entire organization, including the brain's memory, would then be re-created on a digital-analog computer.

To do this, we would need to understand local brain processes, and progress is already under way. Theodore W. Berger and his coworkers at the University of Southern California have built integrated circuits that precisely match the processing characteristics of substantial clusters of neurons. Carver A. Mead and his colleagues at the California Institute of Technology have built a variety of integrated circuits that emulate the digital-analog characteristics of mammalian neural circuits.

Developing complete maps of the human brain is not as daunting as it may sound. The Human Genome Project seemed impractical when it was first proposed. At the rate at which it was possible to scan genetic codes 12 years ago, it would have taken thousands of years to complete the genome. But in accordance with the Law of Accelerating Returns, the ability to sequence DNA has been accelerating. The latest estimates are that the entire human genome will be completed in just a few years.

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EDMOND ALEXANDER

The author argues that neural implants will confer on humans an important advantage that only machines now possess: instant downloading of knowledge. Memories of events could be played back exactly as they occurred, rather than being colored by emotions. Simulations could make fantasies indistinguishable from reality.

By the third decade of the 21st century, we will be in a position to create complete, detailed maps of the computationally relevant features of the human brain and to re-create these designs in advanced neural computers. We will provide a variety of bodies for our machines, too, from virtual bodies in virtual reality to bodies comprising swarms of nanobots. In fact, humanoid robots that ambulate and have lifelike facial expressions are already being developed at several laboratories in Tokyo.

WILL IT BE CONSCIOUS?

Such possibilities prompt a host of intriguing issues and questions. Suppose we scan someone's brain and reinstate the resulting "mind file" into a suitable computing medium. Will the entity that emerges from such an operation be conscious? This being would appear to others to have very much the same personality, history and memory. For some, that is enough to define consciousness. For others, such as physicist and author James Trefil, no logical reconstruction can attain human consciousness, although Trefil concedes that computers may become conscious in some new way.

At what point do we consider an entity to be conscious, to be self-aware, to have free will? How do we distinguish a process that is conscious from one that just acts *as if* it is conscious? If the entity is very convincing when it says, "I'm lonely, please keep me company," does that settle the issue?

If you ask the "person" in the machine, it will strenuously claim to be the original person. If we scan, let's say, me and reinstate that information into a neural computer, the person who emerges will think he is (and has been) me (or at least he will act that way). He will say, "I grew up in Queens, New York, went to college at M.I.T., stayed in the Boston area, walked into a scanner there and woke up in the machine here. Hey, this technology really works."

But wait, is this really me? For one thing, old Ray (that's me) still exists in my carbon-cell-based brain.

Will the new entity be capable of spiritual experiences? Because its brain processes are effectively identical, its behavior will be comparable to that of the person it is based on. So it will certainly claim to have the full range of emotional and spiritual experiences that a person claims to have.

No objective test can absolutely determine consciousness. We cannot objectively measure subjective experience (this has to do with the very nature of the concepts "objective" and "subjective"). We can measure only correlates of it, such as behavior. The new entities will appear to be conscious, and whether or not they actually are will not affect their behavior. Just as we debate today the consciousness of nonhuman entities such as animals, we will surely debate the potential consciousness of nonbiological intelligent entities. From a practical perspective, we will accept their claims. They'll get mad if we don't.

Before the next century is over, the Law of Accelerating Returns tells us, Earth's technology-creating species—us—will merge with our own technology. And when that happens, we might ask: What is the difference between a human brain enhanced a millionfold by neural implants and a nonbiological intelligence based on the reverse-engineering of the human brain that is subsequently enhanced and expanded?

The engine of evolution used its innovation from one period (humans) to create the next (intelligent machines). The subsequent milestone will be for the machines to create their own next generation without human intervention.

An evolutionary process accelerates because it builds on its own means for further evolution. Humans have beaten evolution. We are creating intelligent entities in considerably less time than it took the evolutionary process that created us. Human intelligence—a product of evolution—has transcended it. So, too, the intelligence that we are now creating in computers will soon exceed the intelligence of its creators.

ABOUT THE AUTHOR

RAY KURZWEIL is CEO of Kurzweil Technologies, Inc. He led teams that built a pioneering print-to-speech reading machine, the first omni-font ("any" font) optical-character-recognition system, the first text-to-speech synthesizer, the first music synthesizer capable of re-creating the grand piano and the first commercially marketed large-vocabulary speech-recognition system.

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TWEAKING THE GENETICS OF BEHAVIOR

How might new advances in behavioral genetics affect you and your children? A fictional couple plays design-a-baby. **By Dean Hamer**

SYD AND KAYLA had wanted to be parents for a long time, so when they sat down at their computer to enter the specifications for their new baby, they didn't hesitate. They logged on to SEED (Society's Ethical Engineering Department's Web site) and eagerly began the task of entering their decisions. Because Syd and Kayla were both women, they were going to clone a baby, and because Syd was the better-looking of the two, they had chosen to start with her genes. The child, a girl, would have Syd's comely features and lean build. But thanks to a technique called homologous gene replacement, she would also have the genes for Kayla's coloring and fine set of teeth cut-and-pasted into Syd's DNA. Syd and Kayla chose an adult height for their daughter of six feet—knowing that tall, thin women still seemed to have an advantage, even in the year 2250.

Now came the tough part: selecting the child's personality and temperament. Fortunately, Kayla was an expert in human behavioral genetics; indeed, she was in the midst of writing a history of the subject from the turn of the millennium for *Scientific Terran* (formerly known as *Scientific American*). Kayla's grasp of the crucial yet limited role of genetics in determining human behavior gave her a realistic view of what designing a baby was all about. The fact was, raising children wasn't all that different than it had been 250 years ago. Kayla knew that despite her choice of genes, a good home and the best education, a lot was left to pure chance. Experience and environment would richly texture her daughter's personality, and much of that life history would be a matter of serendipity.

Nevertheless, there were certain qualities Syd and Kayla could control to varying degrees. Just as medical advances in the 20th century had wiped out many deadly diseases, genetic advances in the 21st century had eradicated many forms of psychosis, addictions and just plain unpleasant behaviors. For Kayla, deciding to eliminate as many as possible of the disagreeable surprises that might be lurking in Syd's genes was easy. Targeted intervention seemed far less of a crapshoot than the old approach of meet, mate and procreate—talk about genetic experimentation! But she had to admit that the basis for some behaviors was not yet fully understood. In truth, behavior prediction through genetics remained as much art as science.

Figuring out the human genome sequence—determining the exact order of the more than six billion DNA bases that make up and separate the tens of thousands of genes in every human—had been accomplished early in the 21st century. (The project was actually completed sooner than the government had expected, as a result of the spontaneous collaboration of several major biotech firms, which snapped up patents on every gene they could find.) Enumerating all the genes and learning the mechanics of the proteins they encode took another 20 years after that. But deciphering the cellular and developmental functions of these proteins had taken until the turn of the 22nd century to complete. And scientists were still struggling to fathom how the trillions of possible gene combinations work together to influence the entire range of human behavior. Syd and Kayla could calculate the probability that their child would have a particular behavioral peccadillo—a tendency to oversleep, a taste for strange foods, a penchant for taking risks such as skinny-

Altruism and **happiness** were two of the **traits** that Syd and Kayla were **allowed to select** for their new **baby**.

ALL PHOTOGRAPHS BY CAMELOT *Photonica*; PHOTOILLUSTRATION BY SLIM FILMS

Geneticists are deciphering the molecular underpinning of dozens of behavioral traits, from aggressiveness to shyness. In the future, couples who want children might be able to decide on more than just the baby's sex.

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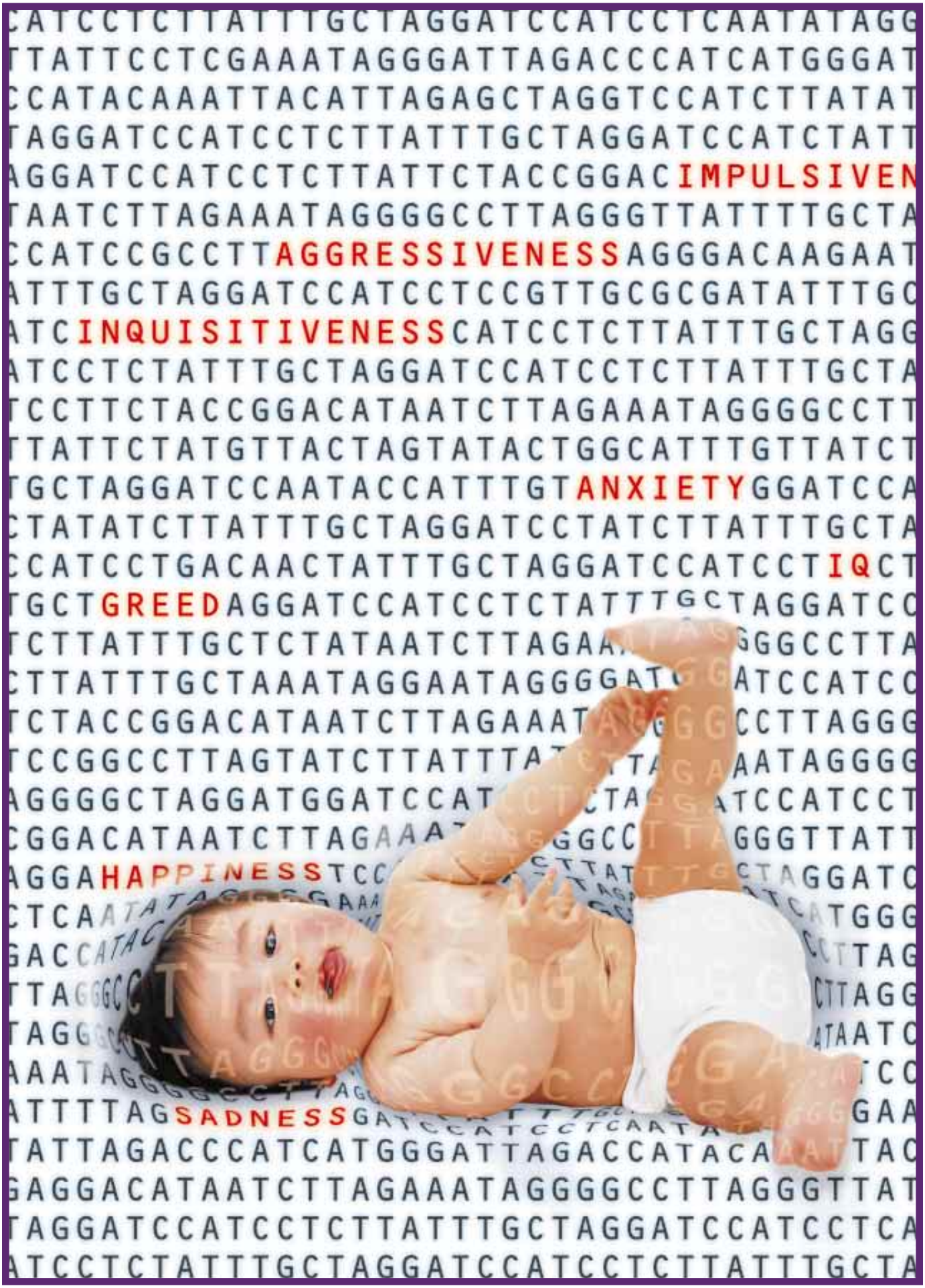

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dipping—but they could not precisely predict her behavior at too detailed a level. As a scientist, Kayla could live with this uncertainty, but the whole undertaking had Syd a little worried.

One thing scientists did know by 2250 was that more than half of a person's genes are involved in shaping behavior. This wasn't surprising, because it had been understood even in the 20th century that more than 50 percent of genes are copied into messenger RNA—turned on, as it were—in the brain. At first, the researchers had tried to determine what all these brain genes did using an old-fashioned "one gene, one behavior" model, but they didn't get very far. The link between brain function and behavior turned out to be far more intricate.

The first breakthrough came when scientists determined the sequence of all the genes of humankind's closest relative, the chimpanzee. As far back as the 20th century, scientists had known that these primates are almost genetically identical to people, with only a 1 percent disparity between the two. By exploring the specific genetic differences, scientists of the 21st century had pinpointed the regions of the human genetic complement responsible for the most human traits, such as cognition, intelligence and consciousness. Geneticists had long suspected that when it came to these characteristics, people simply had different genes than other primates. They were wrong. Most of the variations were found not in the DNA sequences that carry the instructions for building proteins but rather in the snippets of DNA that control whether individual genes are read out. Remarkably, being human was determined more by where, when and how much protein the genes make than by the types of proteins they produce. Humans were even closer to their primate cousins than anyone had guessed. Kayla thought this was beautiful; Syd told her to please stop comparing their daughter to monkeys.

The next big advance in understanding and manipulating the genetics of behavior was helped along by another animal—humanity's best friend, the dog. People had been breeding dogs for thousands of years to emphasize useful traits such as speed, vigilance and an uncontrollable desire to herd things like sheep. Dogs had become tightly inbred; the purebred strains were much more identical genetically than were humans, so genetic mapping in dogs was much easier than in humans. Scientists hit pay dirt in the 21st century, when they were able to identify and then insert a cluster of behavioral genes from a Siberian husky into a greyhound—making a new breed, the greyhusk, which combined the speed of a greyhound with a sled dog's capability for teamwork and harmony. (Several harrowing Iditarod races later, humans finally learned how to cope with the "improvement.")

The information and techniques gleaned from studying chimps and dogs laid the groundwork for a revolution in human behavioral genetics that Syd and Kayla were about to tap. Much of the early work in the 22nd century had focused on intelligence. With bright young women already selling their eggs for tens of thousands of dollars in the late 1990s, there had been no question of a vast and lucrative market for "smart" genes. And researchers quickly confirmed what some scientists had long suspected: intelligence is one of the most heritable human traits.

Studies of twins—Twins!?! Better double-check that part of the form now, Kayla thought—conducted during the 20th century

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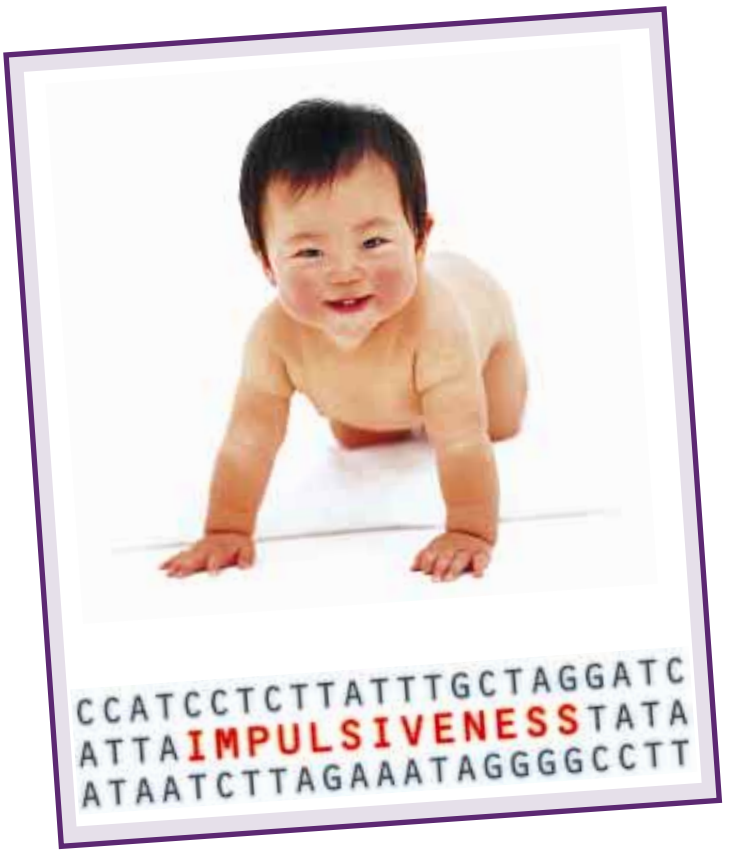
had suggested that genes are responsible for perhaps half the variation in the old-style IQ test scores. (The genetic contribution to IQ appeared to be stronger in older people, whereas younger ones seemed more malleable.) But in the past 250 years scientists had found that the genetic architecture of intelligence was incredibly baroque. They had identified more than 10,000 different genes that contribute to intelligence. And although there were clearly many simple ways to lower IQ drastically, no change in any individual gene had been found to raise it by more than a point—and most added much less than that.

Thousands of the genes involved in intelligence had turned out to code for housekeeping enzymes—ho-hum proteins involved in the everyday maintenance of cellular metabolism throughout the entire body, not just the brain. Because the brain is so delicate, minor genetic changes that throw metabolism even the slightest bit out of kilter alter its function. Although researchers did discover some genes that were specific for human intelligence, these showed remarkably little variation from one person to the next. All people, from the smartest to the dumbest, had these genes. It was the fine-tuning, not the basic construction of the brain, that was controlled by genetic variation. This news had spelled ruin for many a gene-tech start-up company; so far there wasn't much anyone could do to improve intelligence genetically. The real advances had come in the form of cybernetic devices that were implanted within the brain to enhance its function. If Syd and Kayla wanted their child to be able to recite an entire encyclopedia, they would have to put in a request with the neuroimplant experts, not the geneticists; Kayla made herself a note to do just that.



Undaunted by their defeat in the arena of human intelligence, the gene brokers had moved on to other traits and, by the time Syd and Kayla were placing their order, had discovered other aspects of human behavior that were more amenable to genetic manipulation. Predictably, this development caused much hand-wringing among those concerned about whether this power would be used for good or for evil. By the year 2150, as the technology for gene transfer improved and the possibility of eugenics turned into a reality, world opinion reached critical mass. SEED, an organization with members from every part of the world, was formed to oversee genetic selection for each individual born or cloned. The fees were a bit exorbitant, but because they were used to fund new research, Kayla didn't mind paying.

Altruism and happiness were two of the traits that Syd and Kayla were allowed to select for their new baby. As predicted by sociobiologists 250 years previously, altruism was as much in the genes as in upbringing. Unexpectedly, almost all the contributory genes were pleiotropic, meaning that they influenced more than one trait. The same cluster of genes that controls charity, for example, also turned out to have an effect on greed. Syd and Kayla pondered the choices before them, which ranged from the altruism level of Mother Teresa to the most cutthroat CEO. Typically Syd was leaning toward sainthood; Kayla argued for an entrepreneur. In the end, they chose a level midway between, hoping for the perfect mix of benevolence and competitive edge.

There was an even wider range of choices available for happiness, one of the most popular engineered traits. In 2250 most people were even more interested in leading a fulfilled, happy life than in being "accomplished." The gene peddlers' research had con-

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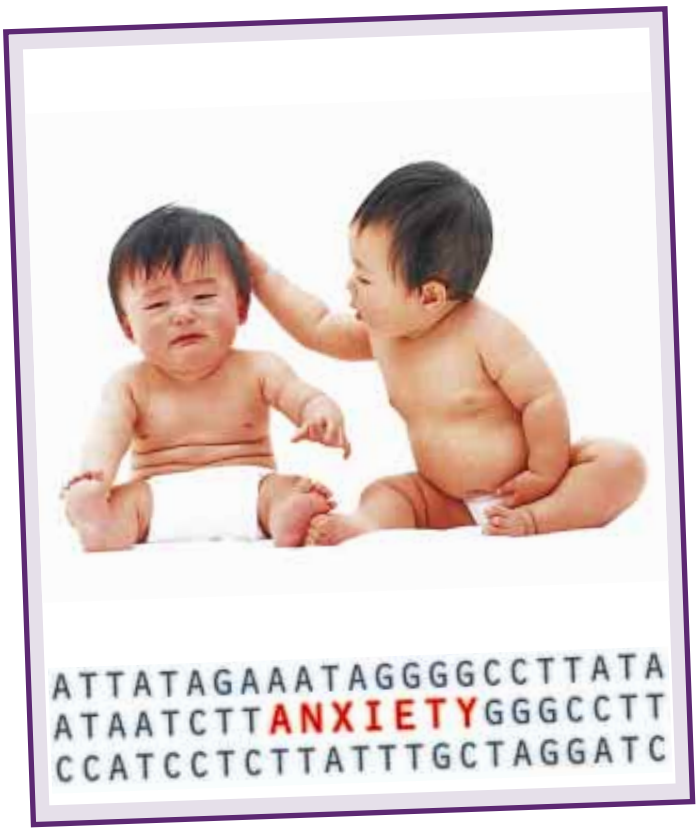
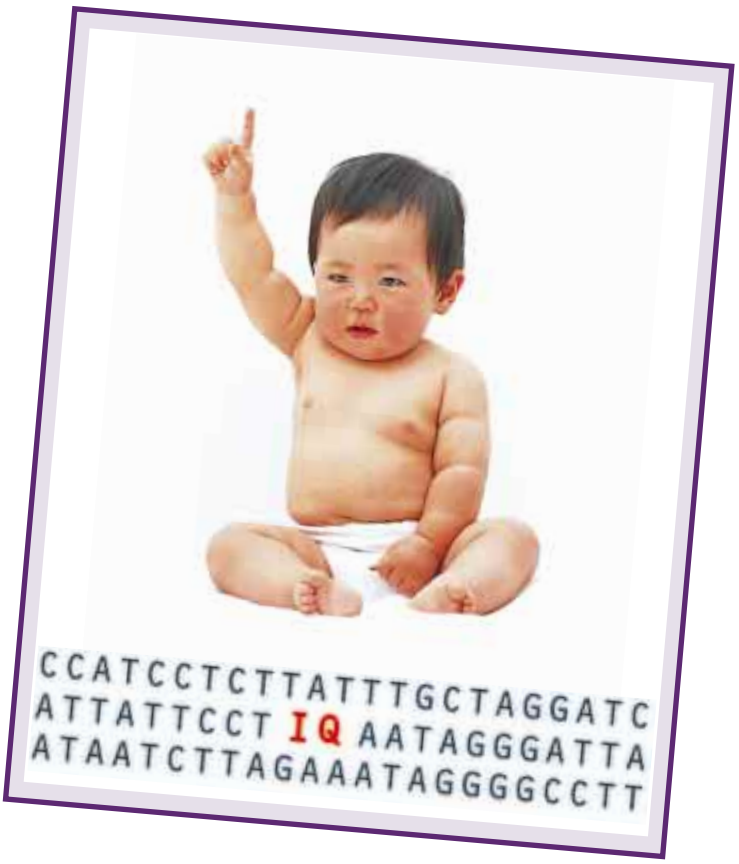
firmed what some scientists in the 1990s had already suspected: happiness was actually affected by two independent physiological mechanisms: one that generated negative emotions and another that led to a positive outlook. Back then, twin studies had shown that genes were probably responsible for about half of a person's tendency to happiness and feelings of well-being; by the time Syd and Kayla were making their decisions, more than 700 such genes had been identified.

Some of the genes coded for enzymes that synthesize and degrade a dozen or so neurotransmitters, chemicals that shuttle signals around in the brain. Others made hundreds of different receptors, proteins on the surfaces of cells that receive chemical signals





from the outside. And then of course there were the genes encoding proteins that interpret the messages within the cells. By fiddling with these genes it was now possible to increase happiness so that, for the most part, people were able to shrug off life's daily annoyances. The words "worrywart," "hypersensitive" and "jerk" weren't used much anymore. Syd and Kayla, however, did not want to set their child's happiness rheostat too high. They wanted her to be able to feel real emotions. If there was a death, they wanted her to mourn the loss; if there was a birth, she should rejoice. Deciding how happy their child would be had been the hardest question they had asked themselves.

Satisfied that their little girl would ride the ups and downs of her life's roller coaster with relative equanimity, Syd and Kayla turned their attention to the more severe forms of mental illness. By now the genes underlying all the classic forms of psychosis had been identified, but this achievement had taken some time. For decades, researchers had searched for the genes responsible for "schizophrenia," a quaint 20th-century term for a mixed bag of brain disorders. They had made little progress until neurobiologists developed elaborate imaging assays to distinguish different subtypes of the disease by their unique neurochemical patterns. Now more than 20 different types of schizophrenia were recognized. Some were primarily genetic, but others were found to be triggered by environmental factors, such as microbes. Other mental disorders—including bipolar (manic-depressive) disease, obsessive-compulsive disorder and attention-deficit hyperactivity disorder—had also been found to have a rich mixture of genetic and environmental causes. Some of these, such as an alteration in a particular receptor in the brain for the neurotransmitter dopamine, had been suspected for centuries, but others, such as the chemical makeup of grilled meat, had come as a complete shock.

This news was disheartening to Syd. She had hoped to engineer away the possibility of mental illness altogether—that had seemed to be one of the upsides of this whole cloning business. But Kayla reassured her that the years of research had also paved the way for hundreds of different drugs, each specifically tailored to compensate for a particular type of genetic defect or environmental damage: what they couldn't eliminate they could almost certainly medicate. This was especially true of the trait that worried Syd the most. At first the couple had hesitated to use her genes at all because of a discouraging trend toward alcoholism in her family.

It was true that most of Syd's immediate relatives had been conceived in a dish and had had at least some remedial gene customization done. And each of them had been preapproved by

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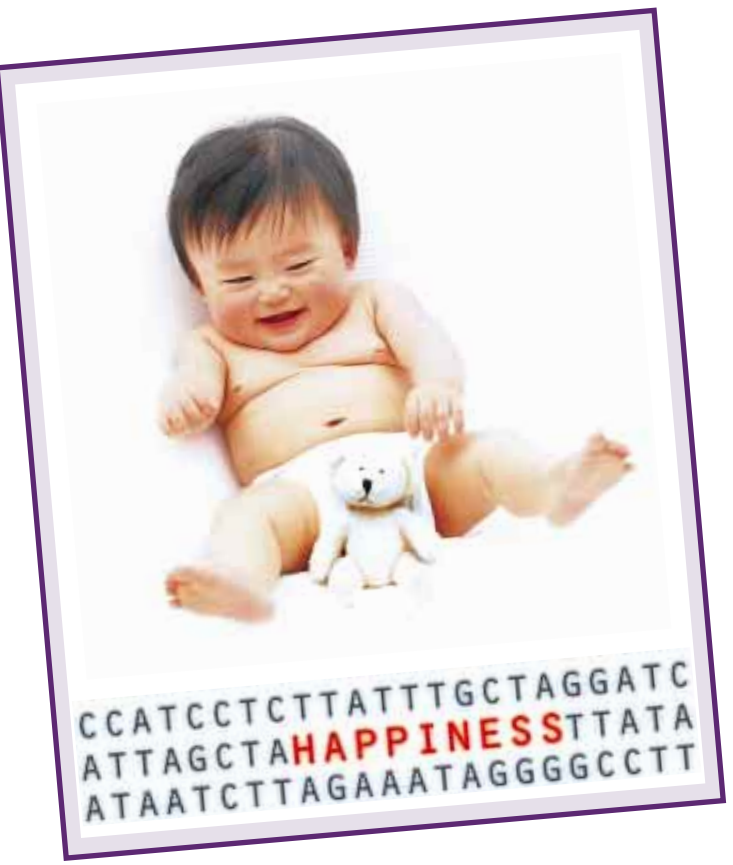
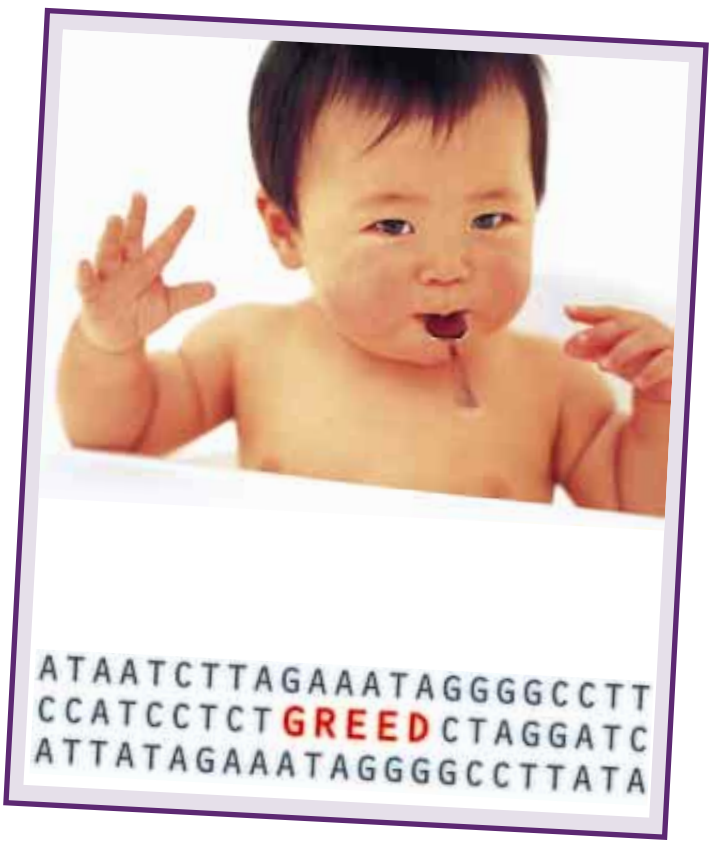
SEED, using Predicti-Chip technology that rapidly screened their genetic blueprint for thousands of potential defects. But Syd's was still a clan of tipplers. Even though scientists recognized centuries ago that alcoholism runs in families, it was only in the past few decades that they had finally identified a suite of genes that predicted with 50 percent accuracy the likelihood a person would become addicted. Although many of Syd's relatives had since been diagnosed with a familial susceptibility to alcohol, they still didn't always steer clear of the stuff, and most had developed the disease. No matter how badly the genetic deck was stacked against them, they refused to believe they could become alcoholics—that much hadn't changed since 2000.

aging had been identified. This made the final years of life far less distressing but had actually extended the average life span only 30 years; as people's biological clocks kept on ticking, their bodies and brains simply wore down by the time they got to be much over 100.

More recently, however, scientists at Methuselah Inc. had succeeded in identifying the genes that acted as the body's basic chronometer. Using genetic methods learned through centuries of tinkering with fruit flies and worms, it was now possible to more than double the average life span of a human to over 200 years. But for the first generation experiencing this longevity, it was a decidedly mixed blessing. Two hundred years was a long time to go on living. Three or four careers and six sets of grandchildren were simply too much. So Syd and Kayla settled on a genetic makeup that would allow their daughter to live for a nice, moderate 115 years.





Syd was relieved to see her own test results: they pretty much guaranteed that her daughter was not going to inherit a vulnerability to alcohol. The inheritance of alcoholism seemed to be attributable to random events during the wiring of the fetal brain. Nothing could be done about that yet, but fortunately an effective antialcoholism drug was now on the market. Soberitin worked by specifically blunting the brain's dopamine-dependent pleasure circuits that were susceptible to alcohol, so that a flute of champagne became no more pleasurable than a glass of water.

Syd and Kayla's little girl would be tall, thin, attractive, altruistic, reasonably happy, and free of alcohol addiction and mental illness. With a life like that, who wouldn't want to live forever? With that thought in mind, Syd and Kayla turned to the longevity section of their order form. By late in the 21st century, the genes for Alzheimer's disease, Parkinson's disease, cancer, heart disease, diabetes and essentially all other common disorders of

Their choices made, they submitted their application and waited for their confirmation number. The technicalities of the cloning would take place the next day, and then Syd and Kayla would confront a human decision that had not changed one iota in the new millennium—what on earth to name the baby.

ABOUT THE AUTHOR

DEAN HAMER is chief of gene structure and regulation at the National Cancer Institute's Laboratory of Biochemistry in Bethesda, Md. He is the author, with Peter Copeland, of *The Science of Desire: The Search for the Gay Gene and the Biology of Behavior* and *Living with Our Genes: Why They Matter More Than You Think.*

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WHEN OFF-THE-RACK BECOMES OFF-THE-NET

Virtual-reality technology, the Internet and computer-aided manufacturing may soon combine to bring custom clothing to your closet. **By Stephen Gray**

MARIA SITS AT HER OFFICE DESK, her mind wandering to powdery Caribbean beaches and azure waters. Her boyfriend, Chris, has asked her to join him in Barbados for his company's Christmas party, but her busy schedule leaves no time to shop for just the right outfit.

Suddenly, she remembers the "smart" card she got at Harrow's, the department store, a few months earlier. The card contains an ultra-accurate three-dimensional digital image of her body, produced on the store's body scanner. The saleswoman said the scan would help them select the best-fitting garments off-the-rack.

At home that evening, Maria logs on to the e-mail address on the card. The Web site's screen shows the pleasing interior of a virtual-reality (VR) store. A voice asks Maria if she wants to select clothes and tells her she can see her scanned body shape if she swipes her smart card through the reader on her personal computer. Maria does and instantly sees a dynamic mannequin of her accurately proportioned virtual body (yes, her behind really is that size), ready to try on virtual clothes.

Maria says she is looking for "a really sexy, sophisticated cocktail dress," and the voice-recognition program allows her mannequin—which moves with lifelike fluidity—to try on dozens of dresses. None of them is exactly right. Frustrated, she turns off the machine and climbs into bed.

The next day Maria logs on and immediately hears from her "personal agent" program, which searches the Internet for her when she is off-line. The personal agent has found Paolo Poniari, a designer near Rome with an amazing collection of dresses, and connects her to his Web site. Clicking on a beautiful dress, Maria is told that this dress was custom-commissioned and is not for sale. Her personal agent interrupts: "Paolo offers a designer service for individual customers," it says. "Shall I connect you?"

After a moment, Paolo himself appears in a video window on-screen. He asks Maria what kind of dress she has in mind, and as she speaks he sketches on a computer screen. She falls in love with the design. Best of all, Paolo guarantees it will be ready in time for the Christmas party and asks Maria to swipe her smart card so he can download her full-body scan.

Five days later Paolo e-mails Maria that he can't get the silk fabric he wants from Thailand in time to cut and ship it to her before her departure. He can, however, have the silk flown directly to Barbados. "I've found a small design studio there," he says. "I'll send the patterns I've made from your body scan, and they'll make it up and deliver it to your hotel room."

"Perfect," Maria says. Seconds later the Internet is alive with traffic: pattern templates and illustrations are sent from Rome to Barbados, cloth orders and delivery instructions go to Thailand, and Maria e-mails Chris to check flight times.

THE VARIOUS TECHNOLOGIES that will enable Maria and Paolo to make this custom fashion transaction are closer than you might think. In fact, some key ones are already in place. Other critical aspects are on the verge of being perfected, and still others are in a preliminary stage of development.

Currently, based on work associated with the Virtuosi program at Nottingham Trent University in England, it is possible to create in-store digital scanning systems that quickly and inexpensively generate accurate 3-D color representations of customers' bodies. Associated hardware and software transform those scans into dynamic, 3-D VR mannequins that can "try on" VR clothes for shoppers and then move around to model them.

Virtuosi, which ran from 1993 through 1996, was created by the university's Computer Clothing Research (CCR) center, of which

MARC PHARES *Epic Studios*

A virtual runway will be a part of a future custom-clothing system. Before ordering a garment, buyers will be able to see how it looks on a virtual mannequin whose proportions are identical to their own. The system will permit views from many different angles and under diverse lighting, and it will accurately depict the "drape" of the garment as the mannequin moves.

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BERND AUERS

Years from now, the first step in ordering a custom garment could be an electronic scan by sensors that precisely measure the contours of the body. The data would then be stored on a smart card, enabling the holder to quickly order made-to-measure clothing anytime off the Internet.

I am director. Intended for use by professional designers, it would enable Paolo to perform most of his job today. It displays a virtual-design studio—complete with interactive in- and out-boxes, filing cabinets and a wall screen for selecting swatches of fabric. Using computer keys or voice commands, designers can choose styles and construct the 3-D garment on static mannequins. This garment can be accurately "unwrapped" into a traditional two-dimensional block pattern that is used to cut cloth. The 2-D pattern can also be translated back into a 3-D garment after changes have been made on it, in order to view their impact on the finished design.

Still impossible, however, is a crucial part of the process: realistically modeling the garment on a moving mannequin to see how the cloth falls and flows while in motion.

TRANSLATING FROM 3-D TO 2-D

The Virtuosi program differs significantly from other attempts at computerized clothing design and display. These earlier efforts, by Cyberware in Monterey, Calif., and Hamamatsu Photonics in Japan, involved capture systems that scan 3-D clothing designs and unwrap them into 2-D pattern templates. Another company, Textile Clothing Technology in Cary, N.C., is developing this technology for made-to-measure goods.

These approaches use static mannequins and depend on point-by-point laser scanning to capture their 3-D clothing templates and the body shape of models or customers. But laser scanning is not commercially viable because it is slow and expensive, requiring prohibitive amounts of computer processing. In addition, the static models in these systems do not allow the clothes to be dynamically evaluated by designers or shown off to shoppers.

Virtuosi uses a less computationally intensive, faster and cheaper digital scanner to capture full-color, 3-D body images, from which the individual's measurements and shape can be extracted. Such a system can also capture images of people with unusual shapes, such as disabled individuals. And it can capture people in different positions, along with the garments they are wearing, to allow animation of the images. The resulting 3-D template is then input into the VR system, where it becomes a mannequin that can be dressed and moved about a virtual showroom by a customer like Maria.

In addition to allowing the design and manufacture of more expensive custom clothing, the Virtuosi system can also bring off-the-rack shopping closer to custom quality. At CCR we are now using its database—which contains 2,500 templates of 3-D body shapes created with the 3-D scanner—to synthesize a range of virtual mannequins that reflect the average bodies of today's women. (We believe this database of 3-D bodies is the largest by far in the world.) The data for the mannequins could be used to manufacture more accurate new dummies for garment makers.

If Maria did not want a custom-made dress, a 3-D scan of her body could be matched against the proportions of these virtual average mannequins, which would allow her to select the best-fitting garment from the rack and view it on her mannequin. Using the

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When **VR custom-wear** arrives, it should **cost** at most **33 percent more** than **off-the-rack.**

3-D scan of her body, one of Paolo's fitters could also identify the closest fit from his stock of 2-D pattern templates and adjust it to the subtleties of Maria's body.

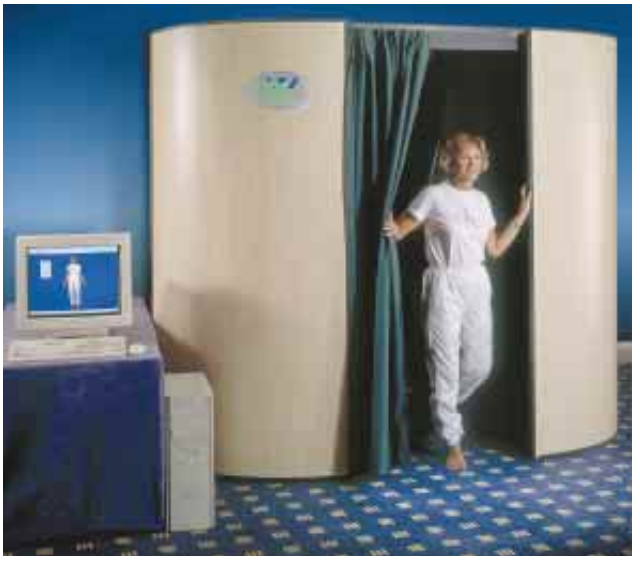
The program's final output is the digital version of the 2-D block patterns used for cutting the cloth. These patterns are intended to be used as input for CAD/CAM (computer-aided design/computer-aided manufacture) systems that actually make the clothes.

CALCULATING DYNAMIC DRAPE

There is, however, more to a fine garment than a good design and the right material, pattern and fit. The garment must move properly when we move, hang well and flow over our body surfaces in a flattering way in order to capture the eye of a discerning shopper like Maria.

This fabric movement is called "dynamic drape" and is the most daunting challenge in computerized fashion design. Whereas fabric characteristics such as yarn structure, fiber content, elasticity and rigidity have been measured and digitized, no commercial modeling system yet exists that can manipulate more than a few of these attributes. Current systems such as Clothreyes, made by Infografica in Madrid, can be used with only very simple, static fabric products such as curtains and tablecloths, which follow very basic shapes.

No one has yet been able to combine fabric properties into a single mathematical model that can yield natural-looking 3-D graphic images. Sueo Kawabata of Shiga University in Japan is doing advanced research on precisely this kind of problem, but his work is still some distance from practical application.



COURTESY OF STEPHEN GRAY

The scanning booth at Nottingham Trent University's Computer Clothing Research center makes templates of three-dimensional body shapes. The booth uses a digital camera to capture the body's frontal outline and side profile, which a computer translates into a digital file in minutes. This template then becomes a three-dimensional virtual mannequin, on which garments can be viewed before they are created.

The reason is that supercomputerlike processing power is needed to model even one piece of cloth draped over a static object. The complexity is significantly multiplied when the cloth is in motion, because the graphic must reflect the effect of every encounter the cloth has with the moving mannequin and with itself. Beyond this, the program must also calculate and represent the effects of the garment's fasteners, linings, seams, padding, facings and stiffeners. Currently such calculations cannot be performed in real time, which makes it impossible to present an animated VR "fashion show."

Our goal at CCR is to find a solution to this problem that will generate cloth with accurate dynamic drape without having to scan and model every mechanical detail of the actual garment. We are now experimenting with the 3-D scanner, using it to capture bodies in different positions while wearing garments, so that the movement of the body and cloth together can be animated to show at least some of the dynamic drape and fit.

Maria and Paolo may be able to make their transaction in about five years, at a reasonable cost. Now that the Virtuosi program has solved the first real challenge—selecting correct fit—there are no major technological hurdles to clear beyond the problem of dynamic drape. A program called MetaStream, from MetaCreation in Carpinteria, Calif., now offers the ability to see all around 3-D objects using a desktop PC, the first step toward 3-D apparel catalogues.

In the end, economics will be the driver. Until the mathematics of dynamic drape are perfected and linked to the 2-D pattern-engineering process, VR custom clothing will be too expensive for the marketplace. Ultimately, VR clothing's timesaving benefits will be the key factor: it can cost $500 to create one sample garment for a product that will retail at $40 and take about 30 days for the various stages in the approval process, such as changing the type of buttons, the shape of a neckline or the design of the fabric. If VR design can speed this up and lower costs, the garment could move into the market more quickly.

When VR custom-wear finally arrives, it should cost just 25 to 33 percent more than off-the-rack apparel. In all likelihood, those kinds of prices will cause a shift in the garment industry, opening the custom clothing market to moderately affluent, time-starved professionals like Maria—a considerably larger clientele than the small coterie of mostly wealthy fashion plates who buy it today. In the notoriously fickle and fleeting world of fashion, this development, unlike most others, will endure. And when it becomes part of our lives, we will all truly look better.

ABOUT THE AUTHOR

STEPHEN GRAY is director of the Computer Clothing Research center and a senior research fellow at Nottingham Trent University in England. Before turning to computer applications in textiles and the arts, he was a command-and-control specialist, writing the graphics software used in the British navy's Opcon system.

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SMART STUFF

The jewelry box of the future could include rings that remember your predilection for vanilla-flavored café au lait. By Kathryn S. Brown

ROSALIND PICARD never realized just how much she squints—until her headband told her. Brooding in Boston traffic recently, waiting for a wall of cars to grind forward, Picard could hear the insistent beeps of a tiny sensor tucked inside a band worn around her forehead—each beep a signal that she had just furrowed her brow in frustration. It's biofeedback as fashion statement. And it's coming to a store near you.

As a scientist at the Massachusetts Institute of Technology's Media Lab, Picard gets to slip on all kinds of "smart" accessories—earrings that measure blood volume pulses, sandals that gauge skin conductivity and glasses that check facial expression are just a few of the trinkets she and her colleagues have designed. Their goal is to make technology ready-to-wear.

Likewise, academic and industry labs worldwide are designing body sensors that detect changes—whether rising fever or just a glance to the right—and respond by offering the wearer useful information. Hidden inside eyeglasses, watches, rings, belts or shoes, these sensors will monitor stress and vital signs, give you a guided tour and maybe even suggest you radio a friend for a pep talk. And the beneficial baubles could hit store shelves within a decade, scientists say.

Smart accessories build off today's body sensors and mobile computers. Already joggers pound along with heart-rate monitors, and delivery boys pack pocket-size computers. At a Sun Microsystems meeting last year, attendees wore rings with a device called an iButton, which can use Java software to store all kinds of information. Loading their coffee preferences into the ring, Sun's participants could order their favorite brew from a robotic coffee machine. And this, researchers suggest, is just the first step toward a budding technology. Gone is the heyday of clutter—blood pressure cuffs, oversize atlases, instruction manuals. In the future, you'll be able to do it all immediately—and in style.

Chances are, you will see things in a whole new light. At Columbia University, computer scientist Steven K. Feiner is crafting eyeglasses that do more than just help you see. Want to try a restaurant in a foreign city? Glance above the restaurant's doorway, and your glasses will immediately become windows to the Internet, offering you a review of the kung pao chicken or coq au vin served inside. Need some help during a presentation? Look to the right, and your glasses will flash your notes. Tired of thumbing through heavy cookbooks with soufflé on your fingers? Peek past your nose and read the recipe in midair.

A WHOLE NEW WORLD

This is "augmented reality"—a virtual world that adds useful sights, sounds and other sensations to your usual horizon. Today Feiner's eyeglass prototype is a headset that looks like ski goggles, wired to both a handheld computer, which runs an Internet Web browser, and a bulky backpack computer, which tracks the wearer's position using a refined Global Positioning System (GPS) receiver. Students who don't mind stares have tried out the *Star Trek*–like ensemble on Columbia's campus. Looking at a building, the wearer sees text labels overlaid on its surface, with a menu that offers information about the building's architecture, the departments inside or the campus location.

Like tape recorders and headphones, Feiner says, these head-worn displays will get smaller, lighter and smarter as technology improves. Already, small companies such as MicroOptical Corporation in Westwood, Mass., are developing lightweight eyeglasses connected to handheld computers about the size of a Walkman.

With funding from the U.S. Army, MicroOptical has designed glasses that display information from a notebook or wearable computer. Soldiers might use the glasses to communicate with army staff or to check their surroundings. Similarly, repair workers who fix airplanes or cars while wearing the glasses could do without notebooks full of instructions. And down the line, when the glasses have finer resolution and tracking devices, doctors might even use them during surgery.

Patients could set the trend for a line of smart accessories, in fact. At M.I.T., mechanical engineers Haruhiko Asada and Boo-Ho

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These futuristic prototypes of smart accessories (*left to right, top to bottom*) do more than just look rad. With the flick of a wrist, a fingernail sensor can direct a robot. Earrings check stress via the body's blood volume pulse. A running bra measures respiration rate and muscle tension. His-and-hers eyeglasses record furrowed brows that can signal interest or confusion. A shoe tracks skin conductivity, another sign of stress. A glove doubles as a computer text editor. And a ring silently records the wearer's vital signs, contacting a physician by computer if necessary.

PHOTOGRAPHS BY SAM OGDEN

Yang have crafted a ring with tiny sensors that measure the wearer's pulse rate and blood oxygen levels. A wireless transmitter inside the ring sends these vital signs to a receiver and, in turn, to an Internet-linked computer in the patient's home, which reads the signs and e-mails a doctor if anything seems awry. And scientists at Sontra Medical in Cambridge, Mass., are developing an ultrasound system that might fit inside a watch to measure blood glucose quickly and painlessly in diabetic patients.

Every fashion has an avant-garde collection, and smart accessories are no exception. M.I.T. chemical engineer Robert S. Langer and his colleagues this year unveiled a new microchip that could release drugs slowly—or, if tucked inside a ring, give off different scents according to a person's mood. Rather than wear her favorite Chanel all day, a woman using this ring might send off sweet pulses of other perfumes as her body temperature and skin conductivity change. It is perfume with a purpose, if there's a love interest nearby—particularly if it contains a human pheromone [see "Nosing Out a Mate," on page 52].

Ultimately, shoppers—not scientists—will determine which smart accessories succeed, Feiner notes. The trinkets should be easy—and pleasant—to use. Researchers can now show off gloves that detect motion, allowing a person to change data on a computer screen, for example. "But have you ever smelled an unwashable glove that a graduate student wears every day?" Feiner asks. "This, as we say, is a nontrivial issue."

And vanity may prevent some people from donning glasses, no matter how clever. Engineers, however, are prepared for that. Some are interested in crafting augmented-reality contact lenses and binoculars. In fact, as small computer displays get brighter and cheaper, Feiner says, the screens will quite likely pop up in many a bauble. "Remember how Dick Tracy used a wristwatch TV for conferencing?" he asks. "That's going to happen. Soon."

ABOUT THE AUTHOR

KATHRYN S. BROWN is a freelance writer who lives in Columbia, Mo. Her smartest accessory is a mood ring that turned permanently green seven years ago.

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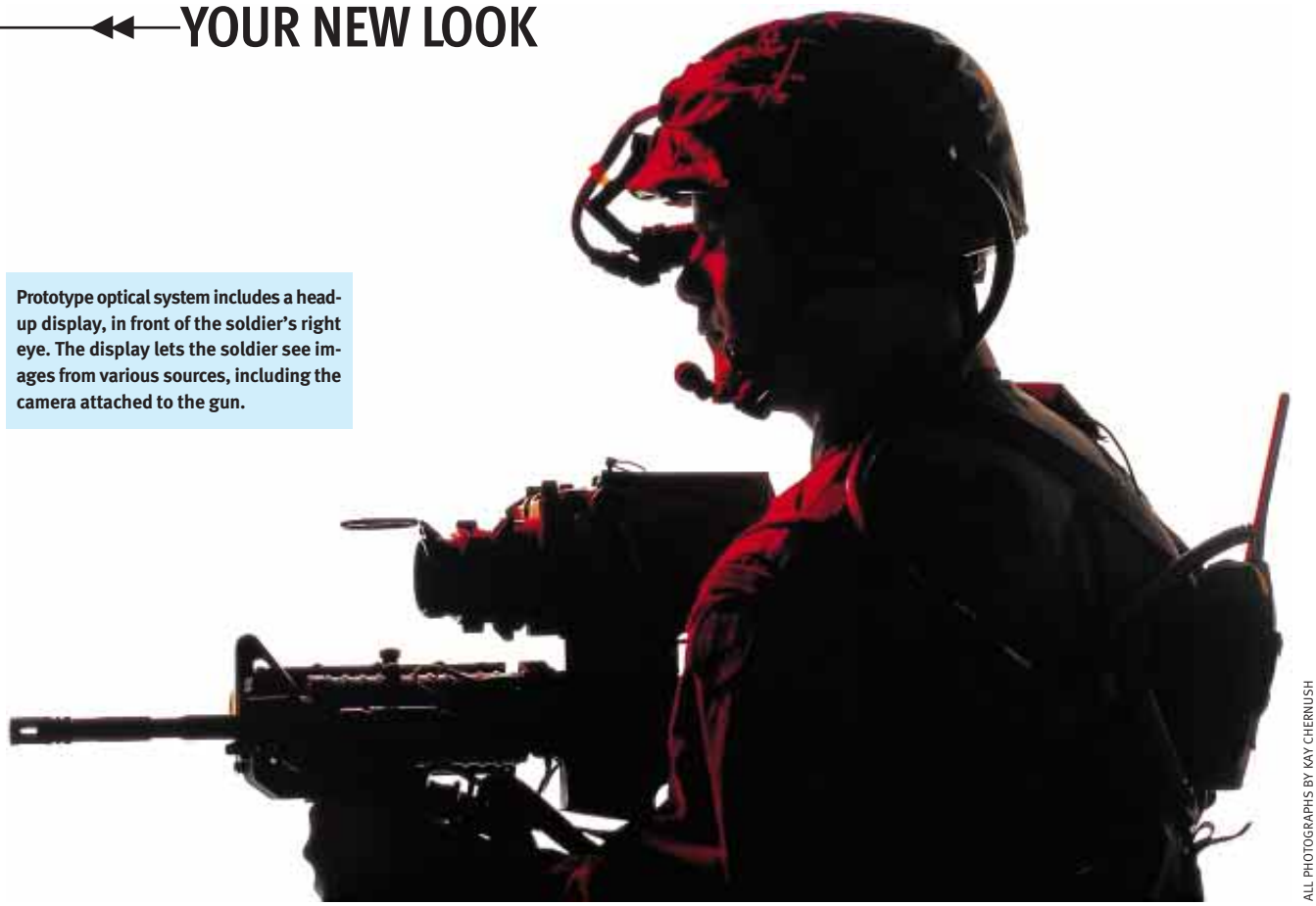

Prototype optical system includes a head-up display, in front of the soldier's right eye. The display lets the soldier see images from various sources, including the camera attached to the gun.

ALL PHOTOGRAPHS BY KAY CHERNUSH

WHAT THE WELL-DRESSED WARRIOR WILL WEAR

Power-generating, chameleonic clothes, food made from bugs and leaves, and tiny robotic scouts may assist the soldier of the next century. **By Steve Nadis**

YOU'RE ALONE, trapped behind enemy lines. You've got your wits to rely on—plus more gadgets than James Bond ever dreamed of. First you unleash a squadron of insect-size robots with tiny cameras to survey the area for hidden threats. Your chameleonic outfit automatically blends in with the surroundings, and its interactive textiles employ "stealth" technology to make you invisible to enemy sensors. And if all else fails, you've still got holographic decoys to confuse the enemy and viruses to disrupt its computers.

Sound far-fetched? Not to the U.S. Army Soldier Systems Center (SSCEN) in Natick, Mass. The center's 550 engineers, technicians and scientists are working on an array of technologies to feed and clothe soldiers, to make them more lethal and mobile, and to help them survive serious injury.

FUTURE MESS: BUG McNUGGETS

If an army marches on its stomach, as Napoleon Bonaparte is supposed to have said, it is Gerald Darsch's job to come up with the lightest, most advanced fuels. Darsch, a project director in the Combat Feeding Program, dreams of high-density rations the size of a deck of cards that would provide a soldier's nutritional and caloric needs for a full day. He hopes these so-called smart foods, or "nutraceuticals," will not only feed soldiers but also boost their immune systems and alleviate stress. During intense conflicts, when troops would not even have time to eat, they could be sustained by a device known, unappetizingly enough, as a transdermal nutrient delivery system. Its sensors would assess the individual's nutritional status, and a patch would administer through the skin the needed vitamins, minerals, amino acids and sugars.

High-tech vending machines, airlifted to troops in the field and powered by microwaves beamed from satellites, would dispense "mission-appropriate" rations. In addition, groups of soldiers would be equipped with "biodigesters" that could convert available ingredients, such as grass, leaves, bugs and worms, into nutritious, if not exactly sumptuous, meals.

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Although none of Darsch's futuristic fare exists today, he thinks some will be available by 2025. "If it took McDonald's 10 years to field Chicken McNuggets," he shrugs, "it could take us even longer to field this."

The army is also taking a long-range view with regard to shielding its warriors from water, heat, cold, bullets, and even chemical and biological agents. Plans call for outfitting soldiers in lightweight, so-called reactive garments whose microscopic fibers will be treated to give them various properties. Using a technique called electrospinning, SSCEN chemist Heidi Schroeder-Gibson has produced a thin polymer shell, which could be fashioned into a body glove that would act as a protective second skin. Though composed of the tiny fibers, the shell has the consistency and texture of a balloon. According to Schroeder-Gibson, "we could put a lot of things in those fibers"—carbon to absorb toxic chemicals, enzymes to break down nerve agents, and environmental sensors—"depositing them in different layers to give the garments the features we want."

Researchers at the center think the polymer shells could form the basis of sensate liners in which a built-in network of sensors, fiber-optic wires and other conductive fibers would ascertain whether a soldier has been wounded and determine the location of the wound, the amount of blood lost and other vital signs. The liner would forward the findings immediately to a command center, where medical evacuation teams would be dispatched.

A helmet-mounted display permits seeing—and aiming—around corners (*above*). The soldier can also call up maps (*right*) that pinpoint the locations of nearby friendly and hostile forces.

In fact, a garment capable of detecting the penetration of the human torso was first demonstrated in 1995, according to Eric Lind, an electrical engineer at the Space and Naval Warfare Systems Center in San Diego. The garment, which has not yet been clinically tested, works by sending light through a closed fiber-optic loop. "If the pulse of light comes back, you know the torso hasn't been penetrated," Lind says. But once the circuit is broken by a bullet, tiny ultrasound microphones embedded in the garment can trace the bullet's path.

A similar approach could lead to garments that change colors, chameleonlike, to match their surroundings: a material's color would be based on the color of light coursing through its fiber-optic threads. "It's possible to do that now," Lind points out, "but we need practical ways of supplying power."

SSCEN specialists are addressing that challenge, too, and not just for the color-changing clothes. They recently started work on a photovoltaic membrane made of conductive polymers that can convert sunlight into electricity. A potential advantage is that the small fibers would give the membrane a surface area some 200 times larger than that of a conventional sheet of comparable size. Others are investigating the possibility of shoes with piezoelectric devices that would generate electricity when their wearer walks.

Lind notes that the nonmilitary market for high-tech clothing could eventually be enormous. Who knows what the fashion world will make of cloth that can change colors on demand? And reactive garments would have obvious applications in law enforcement, firefighting and medicine.

FIRING AROUND CORNERS

In another project with spin-off potential in law enforcement, the army has developed a high-tech protective helmet with a head-up display (no pun intended) that shows the wearer where the friendly and hostile forces are. This display can even be linked to the soldier's weapon, explains SSCEN team leader David Cheney, so that "he could put the weapon around a corner and engage a target without putting himself at risk."

For the longer term, the well-dressed warrior might even sport a "stealth" uniform that alters the wearer's heat emissions and radar-surface signature to blend in with those of the background. Other investigators contemplate in-stride mine detection devices that would instantly alert soldiers to land mines in their midst. Even further out, microrobots that could reliably survey an area and portable devices for creating holographic decoys both await fundamental technological advances.

While no one disputes the tremendous advantages that sophisticated technologies such as these could confer, their high cost could ensure that some, perhaps most, are never issued in large numbers. Estimated costs for outfitting the soldier of 2002 with early versions of a helmet, protective clothing, weapons, and a computer and radio system run about $70,000. Cheney, however, cites $1-million cruise missiles and $100-million tanks in arguing that more money should be spent on the troops themselves.

Political factors will ultimately determine how much of this high technology trickles down to the grunts on the ground. But it is already becoming clear that the next wave in military equipment could very well be personal, literally enveloping the soldiers of the next century in technology.

ABOUT THE AUTHOR

STEVE NADIS is a freelance writer living in Cambridge, Mass. His killer instinct is limited to barbarous games of cribbage.

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WILL WE BE ONE NATION, INDIVISIBLE?

Racial tensions will ease and disparities will narrow, but experts disagree on whether racism will disappear even in 100 years. **By Bruce Agnew**

NEARLY 100 YEARS ago the African-American scholar W.E.B. Du Bois predicted that the challenge of the 20th century would be "the problem of the color line." Echoing Du Bois, historian John Hope Franklin, who headed the advisory board of President Bill Clinton's 1997–98 Initiative on Race, wrote recently, "I venture to state categorically that the problem of the 21st century will be the problem of the color line."

Will we solve it this time around?

No, say many who have studied, worked against and lived with racism. "I would think people sitting down in 2099 will say, 'Well, how much progress have we made? And how much longer do we have to go?'" says Roger W. Wilkins, who headed the Justice Department's Community Relations Service during the Lyndon B. Johnson administration and now teaches history at George Mason University. "I do not believe that we will have a racially equal society 100 years from now. Antiblack racism is too deep, and it's too entrenched."

Others are more optimistic. Abigail Thernstrom, a senior fellow at the Manhattan Institute and co-author of *America in Black and White: One Nation, Indivisible,* points to growing rates of intermarriage among whites, blacks and other minority groups and predicts, "As we move toward a country increasingly made up of Tiger Woodses, I think this whole mind-set [of racial classifications] is going to crumble over time, and it's going to change public policy."

THE NUMBERS GAME

The difference between the experts is one of perspective—and emphasis—not a quarrel over facts. The facts themselves, the statistical measurements of where U.S. race relations have been and where they are headed, are both heartening and dismaying.

Since the passage of the Civil Rights Act of 1964 and the Voting Rights Act of 1965, African-American and other minority groups have made enormous strides toward equality with whites. More than 40 percent of African-Americans described themselves as "middle class" in 1996, compared with just 12 percent in 1949. About 42 percent of black householders own their own homes; more than 30 percent are suburbanites. About the same proportion of blacks and whites finish high school—nearly 90 percent—and more than 13 percent of blacks older than 25 years of age have completed college, compared with 3 percent in 1960. Nearly a quarter of black families had incomes above $50,000 a year in 1996, compared with 44 percent of white families and about 22 percent of Hispanics. Asian-American incomes exceed those of all other groups.

Harvard University historical sociologist Orlando Patterson was surely right when he wrote in *The Ordeal of Integration* that "the changes that have taken place in the United States over the past 50 years are unparalleled in the history of minority-majority relations."

But a significant proportion of African-Americans have been left behind. More than a quarter of black families live below the poverty line. Blacks are arrested at a rate more than twice their proportion in the population. And about 70 percent of African-American babies were born out of wedlock in 1996 (23 percent to teenage mothers), compared with 26 percent of white babies born out of wedlock. "A social pattern with devastating economic consequences has become the norm in the black community, while it is still the deviant pattern among whites," write Thernstrom and her co-author (and husband), Harvard history professor Stephan Thernstrom, in *America in Black and White*.

So Harvard law professor Lani Guinier—whose 1993 nomination as assistant attorney general for civil rights was blocked by conservative opposition—is right when she calls the landmark civil-

PHOTOGRAPHS BY BRIDGET GEREETY

The future of the U.S. population is rosy—and tawny, dusky and olive. Demographers predict the melting pot will contain an even richer broth as people marry outside their race and ethnicity and have children who can lay claim to a mixture of heritages. The question is, Can we all just get along?

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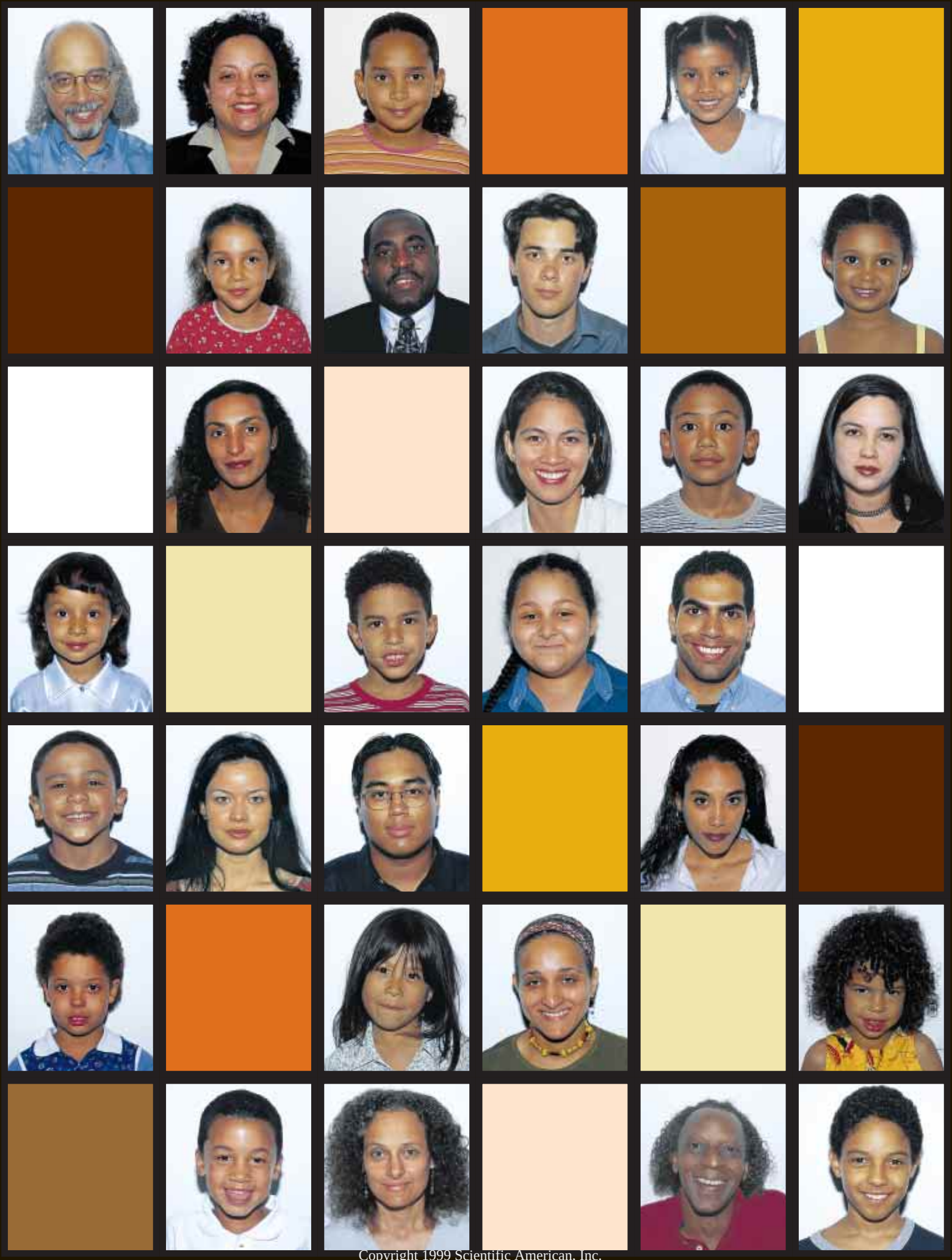

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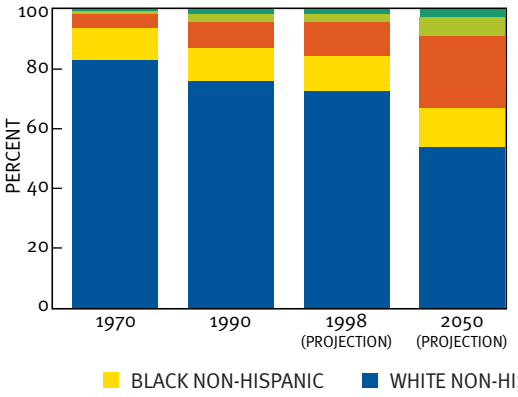
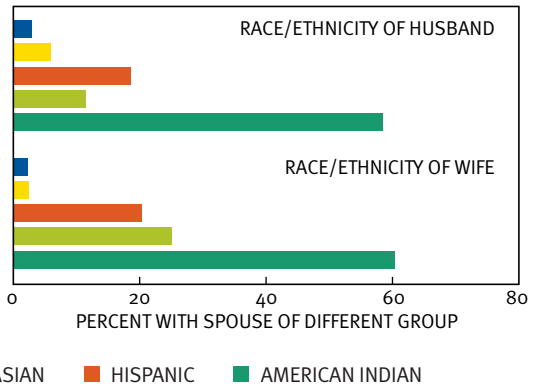
Racial/Ethnic Composition of the U.S.



Marrying across Racial Barriers



The U.S. Census Bureau projects that by the year 2050 non-Hispanic whites will constitute barely a majority of the population at 52.8 percent—and the century will be just half over. Almost two thirds of the population growth between now and 2050 is expected to come from immigrants, their children and their grandchildren.

Interracial marriages are already rising and can be expected to accelerate. "The concepts of race and the language we use to discuss our diversity today may change as fast and dramatically as our diversity itself," according to *One America in the 21st Century*, the final report of the Advisory Board of the President's Initiative on Race.

GRAPHS BY LAURIE GRACE; SOURCE: 1990 DATA, U.S. BUREAU OF THE CENSUS

rights laws of the 1960s "a significant step, [but] a baby step." Guinier was branded a "quota queen" in 1993 because of law review publications advocating novel voting procedures, such as so-called cumulative voting, to enhance minorities' electoral clout. Today she says the structures of segregation and voting-rights denial that were torn down in the 1960s "both camouflaged and reinforced tremendous inequities in the distribution of resources, and if we're going to talk about a just society, I think we have a lot of work to do."

Guinier and Patterson both consider themselves optimists, however. "If the American people were aware that there are other policy choices, I think that we could create a national will to change," Guinier says.

At least one dramatic change already seems inevitable: sometime in the late 21st century, white Americans will no longer be a majority. Currently about 72 percent of the population is white, 12 percent non-Hispanic black, 11 percent Hispanic, 4 percent Asian/Pacific Islander and 0.7 percent American Indian, Eskimo and Aleut. But by the year 2050, the U.S. Census Bureau projects that whites will account for only 52.8 percent of the population, non-Hispanic blacks 13.6 percent, Hispanics 24.5 percent, Asian/Pacific Islanders 8.2 percent and American Indian, Eskimo and Aleut 0.9 percent. "I think that means that an awful lot of white people will have to make very serious identity adjustments," Wilkins says.

was white and the other was black. By 1997 that figure had nearly doubled, to 311,000. That is equal to only 0.7 percent of married couples in which both partners are white, but it is a more significant 8.4 percent of married couples in which both partners are black. And new marriages are even more biracial: 12.1 percent of new marriages by African-Americans in 1993 were to partners who were members of other races.

"It's amazing how much change we've made," observes Boston University sociologist Alan Wolfe, author of *One Nation, After All.* "In 1967 the Supreme Court ruled Virginia's miscegenation law unconstitutional. If that law were still on the books, Clarence Thomas would be in jail rather than on the Supreme Court."

WHICH BOX DO I CHECK?

The most certain, though possibly least significant, consequence of growing intermarriage is that it will play havoc with Census Bureau racial breakdowns. An increasing number of multiracial Americans—such as, most prominently, golf star Tiger Woods—have balked at the racial classification boxes on survey and other government and business forms. The Clinton administration has now decided that in the year 2000 census, people will be allowed to check more than one racial box. Government racial statistics may never be the same—and as the numbers become

Sometime in the late 21st century, **white Americans** will no longer be **a majority.**

In fact, many Americans are already making surprisingly serious identity and attitude adjustments. Interracial marriage, outlawed in some states as recently as the 1960s, is growing. "We already have half of all Asians marrying non-Asians and half of all Hispanics [marrying outside their ethnic group] by the third generation," Abigail Thernstrom notes. "The black-white intermarriage rate is higher than the Jewish-gentile rate was in 1940. It won't go up at the same rate, but nevertheless, it's going up."

The numbers are still tiny, but the trend is clear. In 1980 there were just 167,000 married couples in the U.S. in which one partner

blurred, the now heated controversies over affirmative action and other race-centered issues may lose some of their force.

But intermarriage and the increasing ease of interracial dating among young people are a signal of a far deeper change in U.S. society. One of the biggest reasons for optimism about the 21st century, according to American Enterprise Institute fellow Dinesh D'Souza, author of *The End of Racism,* is "the very healthy attitude of young people, who are in general much less haunted by the specter of old-fashioned racism."

Interracial marriages (and, to a lesser degree, dating) do not

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affect just the two people involved. Such relationships cannot help but have a ripple effect on each partner's family and circle of friends. Stephan Thernstrom notes, "My cousin is married to a black woman, and that certainly had an enlightening impact on my aunts and my mother and father and my uncle. It had many reverberations throughout the whole extended family."

Of course, intermarriage and interracial dating are only an indirect signal of narrowing economic and social differences. Public opinion polls tell the same story, however. In particular, an unpublished poll by the Gallup Organization last year suggests that African-Americans' lives have improved since midcentury. Seventy-nine percent of black respondents last year said they were satisfied with their standard of living; only 45 percent answered that question the same way in 1963. Eighty-four percent were satisfied with their jobs, compared with only 61 percent of those who responded to a similar question in 1963.

About half of both blacks and whites polled rated race relations as "very" or "somewhat" good, and 83 percent of whites and 80 percent of blacks thought relations between the races had gotten better or at least remained the same over the past year. (The poll, updating a 1997 Gallup study, was based on telephone interviews with 2,004 adults, roughly half of whom were white and half black. Responses from the black and white subgroups could have a sampling error of plus or minus 4 percentage points.)

Although both blacks and whites appeared to believe race relations are improving, the Gallup poll revealed a dramatic gap in their perception of today's reality: whites think race relations are better than blacks do. For example:

- Forty-three percent of blacks, but 76 percent of whites, thought blacks and whites are treated about the same in their communities. Fifty percent of blacks, but only 19 percent of whites, thought blacks are treated "not very well" or "badly."
- Forty-two percent of blacks, but only 9 percent of whites, thought blacks are treated less fairly on the job. Fifty percent of blacks, but 83 percent of whites, thought blacks are treated "the same or better."
- Fifty-five percent of blacks, but only 29 percent of whites, thought blacks are treated less fairly by the police, such as in traffic incidents.

Moreover, in responses that offer some measure of daily slights and insults, 46 percent of blacks said that within the past 30 days they had been treated unfairly in a store, in the workplace, at a restaurant, bar, theater or other place of entertainment, by the police or while using public transportation. Fifty-four percent of black males reported such unfair treatment, adds Jack Ludwig, vice president and research director of Gallup's Social Audits Division.

Still, by most measures, the 1960s civil-rights-movement goal of all races together is closer today than ever before—with one horrific exception: urban poverty.

"I think it's clear that if we were ever to 'solve' the race problem, we'd have a tremendous class problem and that really the race problem is becoming a class problem," says Wolfe, whose 1998 book reported that the views and outlooks of suburban, middle-class whites and blacks are more united by class than they are divided by race.

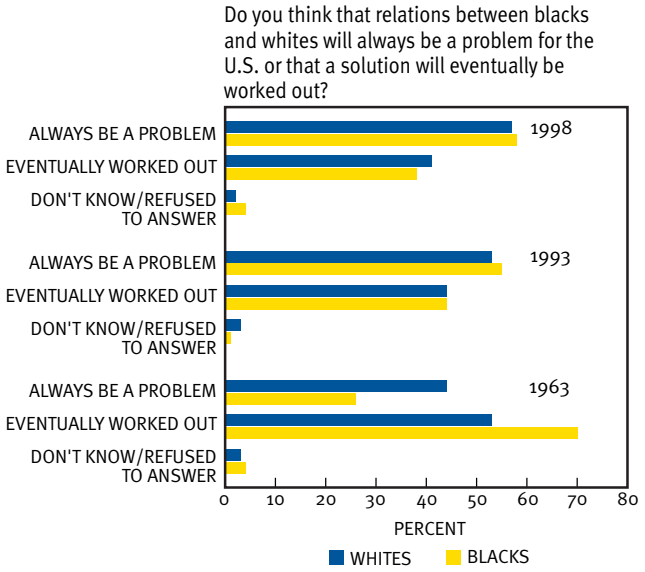
His view is widely shared. "Urban poverty and education are at the top of the want list, the need list, of this country," Franklin declares. Rainbow/PUSH Coalition president Jesse Jackson warned in a 1997 PBS interview that "while there's a focus on the race gap, the bigger gap today is the class gap."

The long U.S. economic expansion of the 1990s has brought a few tentative hints of improvement. Crime rates have dropped for most of the decade. Black unemployment rates and births to teenage unwed mothers have also dipped. But the country has barely begun to scratch the surface of this problem.

When Gallup asked its 2,004 black and white respondents last year whether U.S. race relations would ever be solved, the answer was grim. Fifty-eight percent of blacks and 57 percent of whites said race relations "will always be a problem."

But 100 years is a long time, and there is no reason to think that the 21st century will not bring changes as dramatic as those of the 20th. "We have made enormous progress since 1899, when they were running my grandpa out of Mississippi," Wilkins notes. "They were going to lynch him."

And in 1899, Stephan Thernstrom says, "if you had asked what will be the racial future in the 20th century, people would not have used our racial categories. They would have said, 'Well, let's talk about the Jewish race and the Mediterranean race and the Nordic race,' and that way of thinking has become entirely discredited." Thernstrom believes such "utterly unscientific, 19th-century anthropological concepts [are] not likely to have sway over the American public a century hence."



Whites and blacks appear noticeably less confident today that U.S. race relations will eventually be resolved than they were in late 1963, when the legislation that would become the Civil Rights Act of 1964 was wending its way through Congress. Experience may be a factor: in recent polling, people under age 25 are most likely to say race relations will always be a problem; people over 65 are most likely to say a solution will eventually be worked out.

LAURIE GRACE; SOURCES: 1963 DATA, NATIONAL OPINION RESEARCH CENTER, UNIVERSITY OF CHICAGO; 1993 AND 1998 DATA, GALLUP POLL

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I, CLONE

Sometime, somewhere, someone will generate a cloned human being. What will happen then? **By Ronald M. Green**

DAN WAGNER

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WITHIN THE FIRST FIVE years of the next century, a team of scientists somewhere in the world will probably announce the birth of the first cloned human baby. Like Louise Brown, the first child born as the result of in vitro fertilization 21 years ago, the cloned infant will be showered with media attention. But within a few years it will be just one of hundreds or thousands of such children around the world.

It has been possible to envision such a scenario realistically only since Ian Wilmut and his colleagues at the Roslin Institute near Edinburgh, Scotland, announced in February 1997 that they had cloned a sheep named Dolly from the udder cells of a ewe. The technique used by Wilmut and his co-workers—a technology called somatic-cell nuclear transfer—will probably be the way in which the first human clone will be created.

In somatic-cell nuclear transfer, researchers take the nucleus—which contains the DNA that comprises an individual's genes—of one cell and inject it into an egg, or ovum, whose own nucleus has been removed. The resulting embryo, which will carry the nucleus donor's DNA in every one of its cells, is then implanted into the womb of a female and carried to term.

Such research on the basic processes of cell differentiation holds out the promise of dramatic new medical interventions and cures. Burn victims or those with spinal cord injuries might be provided with replacement skin or nerve tissue grown from their own body cells. The damage done by degenerative disorders such as diabetes, Parkinson's disease or Alzheimer's disease might be reversed. In the more distant future, scientists might be able to grow whole replacement organs that our bodies will not reject [see "Embryonic Stem Cells for Medicine," on page 18].

These important medical uses of cloning technology urge us to be careful in our efforts to restrict cloning research. In the immediate wake of Dolly, politicians around the world proposed or implemented bans on human cloning. In the U.S., President Bill Clinton instituted a moratorium on federal funding for human cloning experiments, and the National Bioethics Advisory Commission urged that the ban be extended to private-sector research as well. Congress continues to study various proposals for enacting such a total ban.

In view of the still unknown physical risks that cloning might impose on the unborn child, caution is appropriate. Of the 29 early embryos created by somatic-cell nuclear transfer and implanted into various ewes by Roslin researchers, only one, Dolly, survived, suggesting that the technique currently has a high rate of embryonic and fetal loss. Dolly herself appears to be a normal three-year-old sheep—she recently gave birth to triplets following her second pregnancy. But a recent report that her telomeres—the tips of chromosomes, which tend to shrink as cells grow older—are shorter than normal for her age suggests that her life span might be reduced. This and other matters must be sorted out and substantial further animal research will need to be completed before cloning can be applied safely to humans.

Eventually animal research may indicate that human cloning can be done at no greater physical risk to the child than IVF posed when it was first introduced. One would hope that such research will be done openly in the U.S., Canada, Europe or Japan, where established government agencies exist to provide careful oversight of the implications of the studies for human subjects. Less desirably, but more probably, it might happen in clandestine fashion in some offshore laboratory where a couple desperate for a child has put their hopes in the hands of a researcher seeking instant renown.

Given the pace of events, it is possible that this researcher is already at work. For now, the technical limiting factor is the availability of a sufficient number of ripe human eggs. If Dolly is an indication, hundreds might be needed to produce only a few viable cloned embryos. Current assisted-reproduction regimens that use hormone injections to induce egg maturation produce at best only a few eggs during each female menstrual cycle. But scientists might soon resolve this problem by improving ways to store frozen eggs and by developing methods for inducing the maturation of eggs in egg follicles maintained in laboratory culture dishes.

It is possible that a **researcher** somewhere in the world is **already at work** on a **human clone**.

Although human cloning could generate a troop of people who look just like you, the clones won't be your age unless they were cloned right after you were conceived. They will still have to grow through childhood and adolescence to adulthood. The big question is: Will society regard them as separate individuals?

WHO FIRST?

Once human cloning is possible, why would anyone want to have a child that way? As we consider this question, we should put aside the nightmare scenarios much talked about in the press. These include dictators using cloning to amass an army of "perfect soldiers" or wealthy egotists seeking to produce hundreds or thousands of copies of themselves. Popular films such as *Multiplicity* feed these nightmares by obscuring the fact that cloning cannot instantaneously yield a copy of an existing adult human being. What somatic-cell nuclear transfer technology produces are cloned human embryos. These require the labor- and time-intensive processes of gestation and child rearing to reach adulthood. Saddam Hussein would have to wait 20 years to realize his dream of a perfect army. And the Donald Trumps of the world would also have to enlist thousands of women to be the mothers of their clones.

For all their efforts, those seeking to mass-produce children in this way, as well as others who seek an exact copy of someone else, would almost certainly be disappointed in the end. Although genes contribute to the array of abilities and limits each of us possesses, from conception forward their expression is constantly shaped by environmental factors, by the unique experiences of each individual and by purely chance factors in biological and social development. Even identical twins (natural human clones) show different physical and mental characteristics to some degree. How much more will this be true of cloned children raised at different times and in different environments from their nucleus-donor "parent"? As one wit has observed, someone trying to clone a future

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Adolf Hitler might instead produce a modestly talented painter.

So who is most likely to want or use human cloning? First are those individuals or couples who lack the gametes (eggs or sperm) needed for sexual reproduction. Since the birth of Louise Brown, assisted-reproduction technologies have made remarkable progress in helping infertile women and men become parents. Women with blocked or missing fallopian tubes, which carry the eggs from the ovaries to the womb, can now use in vitro fertilization to overcome the problem, and those without a functional uterus can seek the aid of a surrogate mother. A male who produces too few viable sperm cells can become a father using the new technique of intracytoplasmic sperm injection, which involves inserting a single sperm or the progenitor of a sperm cell into a recipient egg.

Despite this progress, however, women who lack ovaries altogether and men whose testicles have failed to develop or have been removed must still use donor gametes if they wish to have a child, which means that the child will not carry any of their genes. Some of these individuals might prefer to use cloning technology to have a genetically related child. If a male totally lacks sperm or the testicular cells that make it, a nucleus from one of his body cells could be inserted into an egg from his mate that had had its nucleus removed. The child she would bear would be an identical twin of its father. For the couple's second child, the mother's nucleus could be used in the same procedure.

One very large category of such users of cloning might be lesbian couples. Currently if two lesbians wish to have a child, they must use donor sperm. In an era of changing laws about the rights of gamete donors, this opens their relationship to possible intervention by the sperm donor if he decides he wants to play a role in raising the child. Cloning technology avoids this problem by permitting each member of the pair to bear a child whose genes are provided by her partner. Because the egg-donor mother also supplies to each embryo a small number of mitochondria—tiny energy factories within cells that have some of their own genetic material—this approach even affords lesbian couples an approximation of sexual reproduction. (Cloning might not be used as widely by gay males, because they would need to find an egg donor and a surrogate mother.)

A second broad class of possible users of cloning technologies includes individuals or couples whose genes carry mutations that might cause serious genetic disease in their offspring. At present, if such people want a child with some genetic relationship to themselves, they can substitute donated sperm or eggs for one parent's or have each embryo analyzed genetically using preimplantation genetic diagnosis so that only those embryos shown to be free of the disease-causing gene are transferred to the mother's womb. The large number of genetic mutations contributing to some disorders and the uncertainty about which gene mutations cause some conditions limit this approach, however.

A very large category of users of human cloning might be lesbian couples.

Some couples with genetic disease in their families will choose cloning as a way of avoiding what they regard as "reproductive roulette." Although the cloned child will carry the same problem genes as the parent who donates the nucleus, he or she will in all likelihood enjoy the parent's state of health and will be free of the additional risks caused by mixing both parents' genes during sexual reproduction. It is true, of course, that sex is nature's way of developing new combinations of genes that are able to resist unknown health threats in the future. Therefore, cloning should never be allowed to become so common that it reduces the overall diversity in the human gene pool. Only a relatively few couples are likely to use cloning in this way, however, and these couples will reasonably forgo the general advantages conveyed by sexual reproduction to reduce the immediate risks of passing on a genetic disease to their child.

Cloning also brings hope to families with inherited genetic diseases by opening the way to gene therapy. Such therapy—the actual correction or replacement of defective gene sequences in the embryo or the adult—is the holy grail of genetic medicine. To date, however, this research has been slowed by the inefficiency of the

RODDY FIELD *Roslin Institute*

Cloning seems to have no ill effects so far. Dolly, the first mammal ever to be cloned, gave birth in 1998 to Bonnie, who by all accounts is normal. This past year Dolly delivered a healthy set of triplets.

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ROBERT HOLMES *Corbis*

Cloning will allow lesbian mothers to give birth to a clone of their partner. Gay men would still have to find an egg donor and a surrogate mother.

viruses that are now used as vectors to carry new genes into cells. By whatever means they are infused into the body, such vectors seem to reach and alter the DNA in only a frustratingly small number of cells.

Cloning promises an end run around this problem. With a large population of cells from one parent or from an embryo created from both parents' gametes, vectors could be created to convey the desired gene sequence. Scientists could determine which cells have taken up the correct sequence using fluorescent tags that cause those cells to glow. The nucleus of one of these cells could then be inserted into an egg whose own nucleus has been removed, and the "cloned" embryo could be transferred to the mother's womb. The resulting child and its descendants would thereafter carry the corrected gene in every cell of their bodies. In this way, age-old genetic maladies such as Tay-Sachs disease, cystic fibrosis, muscular dystrophy or Huntington's disease could be eliminated completely from family trees.

CLONING AND IDENTITY

Merely mentioning these beneficial uses of cloning raises difficult ethical questions. The bright hope of gene therapy is dimmed somewhat by the reawakening of eugenic fears. If we can manipulate embryos to prevent disease, why not go further and seek "enhancements" of human abilities? Greater disease resistance, strength and intelligence all beckon alluringly, but questions abound. Will we be tampering with the diversity that has been the mainstay of human survival in the past? Who will choose the alleged enhancements, and what will prevent a repetition of the terrible racist and coercive eugenic programs of the past?

Even if it proves physically safe for the resulting children, human cloning raises its own share of ethics dilemmas. Many wonder, for example, about the psychological well-being of a cloned child. What does it mean in terms of intrafamily relations for someone to be born the identical twin of his or her parent? What pressures will a cloned child experience if, from his or her birth onward, he or she is constantly being compared to an esteemed or beloved person who has already lived? The problem may be more acute if parents seek to replace a deceased child with a cloned replica. Is there, as some ethicists have argued, a "right to one's unique genotype," or genetic code—a right that cloning violates? Will cloning lead to even more serious violations of human dignity? Some fear that people may use cloning to produce a subordinate class of humans created as tissue or organ donors.

Some of these fears are less substantial than others. Existing laws and institutions should protect people produced by cloning from exploitation. Cloned humans could no more be "harvested" for their organs than people can be today. The more subtle psychological and familial harms are a worry, but they are not unique to cloning. Parents have always imposed unrealistic expectations on their children, and in the wake of widespread divorce and remarriage we have grown familiar with unusual family structures and relationships. Clearly, the initial efforts at human cloning will require good counseling for the parents and careful follow-up of the children. What is needed is caution, not necessarily prohibition.

As we think about these concerns, it is useful to keep a few things in mind. First, cloning will probably not be a widely employed reproductive technology. For many reasons, the vast majority of heterosexuals will still prefer the "old-fashioned," sexual way of producing children. No other method better expresses the loving union of a man and a woman seeking to make a baby.

Second, as we think about those who would use cloning, we would do well to remember that the single most important factor affecting the quality of a child's life is the love and devotion he or she receives from parents, not the methods or circumstances of the person's birth. Because children produced by cloning will probably be extremely wanted children, there is no reason to think that with good counseling support for their parents they will not experience the love and care they deserve.

What will life be like for the first generation of cloned children? Being at the center of scientific and popular attention will not be easy for them. They and their parents will also have to negotiate the worrisome problems created by genetic identity and unavoidable expectations. But with all these difficulties, there may also be some novel satisfactions. As cross-generational twins, a cloned child and his or her parent may experience some of the unique intimacy now shared by sibling twins. Indeed, it would not be surprising if, in the more distant future, some cloned individuals chose to perpetuate a family "tradition" by having a cloned child themselves when they decide to reproduce.

ABOUT THE AUTHOR

RONALD M. GREEN is a professor of ethics and director of Dartmouth College's ethics institute. The father of two children, he has no intention of cloning himself in the near future.

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LIVING IN TECHNOLOGY

Powerful microprocessors and the Internet may finally deliver whole-house control. But are you ready for the "therapists of the new millennium"? **By Patrick Joseph**

FANCY A HOME in which the refrigerator knows you're out of eggs and orders them for you from the grocery store? Imagine the television scouring the ether for the types of programs you like and dutifully recording them for you to watch at your leisure. How about a thermostat that takes running stock of the local weather forecasts and adjusts itself in preparation for whatever is coming and a sprinkler system that kicks in whenever necessary to keep your lawn looking like the third green at Augusta National?

Chances are this is not the first time you've read predictions of domestic wonders along these lines. Ever since the 1939 World's Fair, if not earlier, futurists have been telling us that technology will soon eliminate household drudgery. A technology called X-10, which controls home electronic devices by sending command messages in the form of signal bursts across the electrical wiring, has been on the market since 1979. Even the term "Smart House" is a long-standing trademark. But despite improvements in the technology, whole-house control, as it is sometimes known, has largely remained the domain of small, private companies. These generally cater to either the technically inclined hobbyist or to the wealthy, who can afford to hire experts to figure out how to use the typically baffling products now available.

So why might the picture change in the near future? Three factors could finally bring whole-house control to the masses: very powerful microprocessor chips, which are the "brains" of products ranging from personal computers to microwave ovens; the increasing pervasiveness of the Internet; and a growing commitment to home networking among major software and hardware companies.

PUFFED-UP PCs

As we enter what has been dubbed the post-personal-computer era, the line between consumer electronics and computers is growing increasingly blurry. "The future of any appliance is likely to be

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a stripped-down or puffed-up PC," wrote Nicholas Negroponte, director of the Massachusetts Institute of Technology's Media Lab, in his 1995 book *Being Digital*. Microprocessors, like all digital silicon chips, continue to keep pace with Moore's Law, which holds that the number of transistors per unit area of chip is doubling every 24 months. The upshot is that microprocessors and operating systems are becoming much more powerful, and household devices that contain them are growing smarter. The trend seems inevitable: all that computing power will cry out for new applications. Most important, if the home-networking honchos have their way, these smart appliances will function not as stand-alone devices but as players on an in-home network—which, in turn, will connect to the outside world via the Internet.

Though the high-tech help described here may seem decades off, in fact essentially all the technology already exists to make it reality. Frigidaire Home Products, for instance, has teamed up with ICL, an information-technology services provider, to build a prototype refrigerator with a built-in PC and bar-code scanner to track inventory. Several sites on the Internet are already in the business of delivering groceries from their stockrooms to your door. Another smart device on the market today, ReplayTV, employs an intelligent agent to search for television shows based on your preferences and records them to a hard drive.

The weather-conscious thermostat is not here yet, but it would not be hard to build, according to Mike Paull, managing director of intelligent home systems at Microsoft. As he envisions it, the thermostat would tap into the processing power and memory of a PC and monitor the local weather via the Internet, while receiving data on ambient temperatures from sensors around the house.

Internet connections—and communication among the dozens of microprocessors scattered around your home—present all manner of opportunity. Negroponte, obviously a coffee lover, cites the classic example involving the alarm clock and the coffeemaker. Today, if you reset your alarm clock for 6:45 A.M. and the coffeemaker is still programmed to grind the beans and steep the grounds at your usual wake-up hour of six, you will start the day with awful coffee. Which is, of course, a crying shame. But in Negroponte's coffee-friendly vision of the future, the alarm clock will not only confer with the coffeemaker about when to begin brewing, it might also monitor traffic reports from the Internet. Noticing that, say, the commute will be better than usual, it might let you sleep an extra 15 minutes. In the future, the coffee is always fresh and the alarm clock is your friend. At least that's how it ought to be.

Although that may seem a little frivolous as visions go, it's just one small example taken from the gestalt. The wider view involves a whole array of possibilities, including sprinkler systems that know when to water the lawn, lighting that senses your presence in a room and turns itself off when you leave, digital audio and video programs delivered in real time to your multimedia center, and voice-recognition software that responds to your verbal commands.

COMPUTING EVERYWHERE, CONNECTING EVERYTHING

Perhaps the most convincing sign that the age of whole-house control is dawning is the interest of such information technology giants as Cisco Systems, IBM, Intel, Microsoft and Sun Microsystems. Alliances have been formed to deliver high bandwidth across the figurative "last mile" to the home, and divisions have sprung up within companies to champion their vision for the home of the future. Different terminologies have been adopted to describe this concept—some of the current buzzwords are pervasive computing, ubiquitous computing and spontaneous networking. Craig Mundie, senior vice president of the consumer strategy division at Microsoft, calls it the "computing everywhere, connecting everything vision." Whatever the name, the long-range plan is nearly the same: networked homes full of interconnected intelligent devices.

The high-tech companies "see 100 million homes, and maybe 50 percent of them are potential, likely candidates to buy into home networking over the next 10 years," says industry analyst Bruce Kasrel. "So there are 50 million homes where they could sell five, maybe 10 different devices. That's a large potential market." But initially, he says, the money will not be in whole-home connectivity, but in networking multiple PCs in the home to share high-speed Internet connections and peripherals. Kasrel's firm, Forrester Research, is forecasting over $1 billion in sales in the home-networking market by 2002.

Not all industry observers are so enthusiastic, especially in the short term. "This is still a technology looking for an audience," says analyst Rob Enderle of Giga Information Group. "The appliance makers are going to need to see a market before they start building refrigerators with browsers in them. And consumers are going to have to justify the costs to themselves." Grayson Evans, president of

The front of a high-tech beach house (*opposite page*) in California offers no clue about the wonders within. In the central machine room in the basement, equipment racks (*right*) hold an Ethernet hub, phone switching gear, digital dimming controls for all the lights, satellite receiver electronics, the master control unit, and video and audio systems, including an 800-disc CD changer.

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Touch panels scattered throughout the house let the occupants control the lights, the motorized window shades and skylight covers, the audio system and the climate. The illuminated panels are seen here in the kitchen (*left*), the dining room (*center left, top*) and another view of the kitchen (*center right, top*). Near the wet bar (*center left, bottom*), which is in a corner of the media room/library, is a rack of entertainment electronics, including DVD and VHS players and an auxiliary CD chang-

a home-automation consultancy called The Training Dept., agrees, saying that residential-networking technologies will be adopted only incrementally over time. "The consumer thinks this is nice and it's all very interesting, but it's not something that they're demanding or setting aside a budget for."

Stewart Brand, cyberpundit and founder of the *Whole Earth Catalog,* thinks such skepticism misses the point: "The fact that this is not a need is not at all an indicator that there's no market. What innovation is, basically, is creating markets where they didn't exist. And there's great money in that because the first couple in get to control it."

Convinced that consumers are ready for home networks, the high-tech companies are struggling to establish standards for operating in and across the wide variety of communications media most home networks are expected to employ—namely, coaxial cables, phone lines, power lines, and infrared and radio signals. On the software front, Sun Microsystems and Microsoft are already engaged in a code war: Sun is pushing Jini, a Java-like language that will automatically configure components to "announce" themselves to networks. Microsoft's model, called Universal Plug and Play, is based on open standards, including IP, TCP/IP and Extensible Markup Language.

The goal for all involved is to make any networking system simple enough for consumers, many of whose VCRs are still flashing an inexorable 12:00. "It has to be brain-dead simple," says Ed Arrington, marketing manager for the Intel Architecture Lab's home-networking initiative. "Walk up, touch button, there it is. We like to say, 'Nothing to learn and nothing to load.'"

REBOOTING THE KITCHEN

Simple or not, consumers may be suspicious about a home in which the reading lamp has its own Internet address, the alarm clock a mind of its own. Touching on such fears, Michael Schrage wrote a column on smart houses for the *Washington Post* in 1993. Writing in diary form, the journalist adopted the persona of a "totally wired" homeowner, tickled at the idea of having the "smartest house on the block." Predictably, his networked utopia becomes a dystopia in short order. "Yesterday the kitchen crashed," he records, five days into his log. "Turns out the problem was 'unanticipated failure mode.' The network had never seen a refrig-

"Things that were once **obvious and mechanical** are becoming invisible and **mysterious.**"

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er. The large touch screen is the principal controller for the home's CD management system. Elsewhere in the media room/library (*center right, bottom*), a tabletop touch panel controls the room's audiovisual options. It can also convert the room in the middle of the day to pitch darkness in 25 seconds. Behind the house (*right*) a handheld version of the touch panel (*in front of chair*) controls the music system, which emanates from four speakers hidden in the courtyard.

erator bulb failure while the door was open. So the fuzzy logic interpreted the burnout as a power surge and shut down the entire kitchen. But because the kitchen memory sensor confirmed that there hadn't been a power surge, the kitchen's logic sequence was confused, so it couldn't do a standard re-start.... Rebooting the kitchen took over an hour."

In fact, reliability is a real concern, according to Stephen Selkowitz, head of the building technologies department at Lawrence Berkeley National Laboratory. Although Selkowitz and his colleagues see ways in which smart homes will improve energy efficiency as well as comfort, he confesses to worrying that "things that were once obvious and mechanical are now being made invisible and mysterious."

In a multimillion-dollar home on a beach in northern California, the mysteries are kept fairly tidy. In racks in a basement chamber resembling an office-server room stands an impressive array of neatly stacked black boxes—amplifiers, CD players, satellite receivers and a master control unit to tie all the systems together. A small television monitor displays a control interface that the installer, Gary Huff of The Media Room, Inc., accesses with a wireless keyboard. On the walls of the room, gray panels hide the wiring to the lighting controls. Circuitry for the digital phone system is housed in a compact panel by the door. The room is impeccably neat; no Medusa-like chaos of wires anywhere. The back panels of the electronics stack are as orderly as a museum display case.

The rest of the home is similarly impressive. As warmth radiates from the hydronically heated floor, Huff summons music from a small touch screen by the front door. The blues spill out of nowhere. From another touch screen in the living room, he brings the shades down, dims the lights and drops a large projector screen, all with the touch of a button. A projector descends from the ceiling, where it has been deftly hidden, ready to play cable, satellite or DVD selections.

Then a minor glitch. Searching remotely for a particular title from the 800-CD music library, the interface locks up. "No problem," says Huff, unfazed. "It's just a simple reboot." When a visitor remarks that technical help will very likely become the priest class of the future, Huff nods. Taking in the view from his clients' dream home—a tranquil stretch of beach and the white-capped Pacific beyond—he adds his own spin: "They're the therapists of the new millennium."

ABOUT THE AUTHOR

PATRICK JOSEPH is a freelance writer living in Berkeley, Calif. In his idea of a high-tech house, the alarm clock delivers a low-voltage shock, and the coffeemaker buys the beans and brings a steaming cup to the bed.

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DAN WAGNER

FUTURE FEAST

Even the meat and potatoes are being reinvented: the meat could come from a test tube, and the potatoes could ward off cholera. **By Jim Kling**

SNEEZING GENTLY, you ease open the refrigerator door to take stock after returning to town from your summer home. The situation isn't so grim after all: there's that romaine lettuce you bought six months ago, still looking fresh and crisp. A chunk of Parmesan, picked up—what year is this again? And down on the bottom shelf: vegetables of various vintages and, there it is, that nice piece of cooked, shrink-wrapped synthetic chicken. It has been in your refrigerator longer than some of your neckties have been in your closet. Just as you realize that the scratchiness in the back of your throat is not going away, you come across a little bottle of antiviral salad dressing. That clinches it. Chicken Caesar salad it is.

Although that scenario may sound a little strange, tomorrow's world of high-tech foods would most likely seem as fantastic to us as microwaves, frozen meals and today's wide selection of produce would have appeared to a cook just 50 years ago, let alone 100. Many of the details of how food will taste and look, and how it will be packaged and prepared, will depend on that most elusive of intangibles, consumer tastes and preferences. Nevertheless, several trends seem to be gathering momentum, offering glimpses of what and how we might be eating early in the next century.

Blue food? Purple whatsits? Not likely. According to one successful purveyor of engineered foods, edibles with characteristics that deviate radically from current preferences won't catch on with consumers.

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One is the explosive growth lately in sales of dietary supplements and the advent of so-called functional foods, which contain additives that confer physiological benefits beyond simple nutrition. In addition, tasty new forms of protein—including steaks and fillets grown in chambers rather than as part of an animal—as well as packaging that lets produce breathe and treatments that kill harmful bacteria with radiation or pressure are all likely to be a part of the 21st-century dinner table.

SUPERCHARGED FOOD

One of the most remarkable phenomena in nutrition in recent years is the rise of dietary supplements and, in particular, of "sports supplements" aimed at weight lifters and other physically active people. Last year Americans spent about $13.7 billion on dietary supplements, according to Grant Ferrier, editor of the *Nutrition Business Journal* in San Diego. About $800 million of that total was spent on sports supplements, not including sports nutrition bars and electrolyte replacement drinks, Ferrier adds. The category barely existed a decade ago.

Such supplements could be just the first entries in a burgeoning market for supercharged food. "Most of the sports supplements are designed to produce benefits centered on control of body composition and energy," says A. Scott Connelly, chairman and founder of Met-Rx Engineered Nutrition in Irvine, Calif. "People are realizing that the simple calorie theory of body fat control is hopelessly inadequate. For example, supplementing regular dietary intake with lean protein assists the body in burning fat," he maintains.

Connelly further notes that many staple foods such as rice and potatoes are poor sources of vitamins, minerals and other nutrients. Although nutritional supplement companies have long recognized this problem and marketed daily multivitamins and minerals to meet it, "I can tell you as a doctor that human beings don't like to take pills," he insists. "Probably less than 25 percent of people with high blood pressure comply with their prescription. Increasing nutrient density [of traditional foods] has to be a primary goal."

As an example, Connelly cites pizza, "the nutritional Antichrist." Met-Rx's nutritionists have reengineered the humble pizza, the quintessential food for the masses. Each nine-inch pie has 650 calories—rather fewer than a conventional pizza that size would have. Moreover, the enhanced slice contains 75 grams of a high-quality protein—about four times more than usual. It also has 160 percent of the recommended daily allowance of calcium and 300 percent more lycopene. This plant pigment, which gives the tomato its red color, is also an antioxidant that has been linked in some studies to reduced incidence of heart disease and prostate cancer in men. The lycopene comes from a variety of tomato genetically engineered to produce considerably more of the molecule than a normal tomato does.

Where might it all lead? If you are waiting for a nutrient-packed food pill, a favorite of 1950s science fiction, you will be disappointed. Although military researchers are working on a high-density daily ration about the size of a deck of cards [see "What the Well-Dressed Warrior Will Wear," on page 74], such a product is not likely to make its way into supermarkets. According to Connelly, food will have to be "in sync with current taste and texture preferences. We won't be successful in trying to get people to abandon their tastes for sweets and fats."

IMMUNITY-BOOSTING PRODUCE

Another piece of evidence that the age of high-tech foods has arrived was the introduction last May of the margarine Benecol. Its makers say that eaten regularly in sufficient quantities, the product's plant stanol esters can reduce the risk of heart disease by lowering levels of potentially harmful, low-density lipoproteins and increasing levels of healthy, high-density lipoproteins. The margarine is an example of a functional food or "nutraceutical," whose additives provide one or more specific health benefits beyond simple nutrition.

Such foodstuffs could be the basis of an industry raking in $34 billion by the year 2020, Ferrier states. Indeed, they are already carving out a sizable niche in Japan, he adds. Cutting cholesterol would only be the beginning; experts foresee products that would do anything from boosting your immune system to fighting seasonal allergies. For the seriously overweight, for example, there will be foods containing glucagon, a chemical that causes some people to feel full after eating modestly.

Suppose your doctor tells you, 15 years from now, that you've got a mild form of diabetes. Rather than closely monitoring your food intake and blood sugar levels, as you would probably have to do today, you might be able to find everything you need to stay healthy in your local supermarket's health food section. No, not the dreaded row lined with organic granola and sprouts but rather an aisle with foods containing additives that, to continue our example, regulate insulin activity and keep your blood sugar under control.

One researcher is stimulating muscle cells in hopes of growing a filet mignon.

According to John P. Troup, head of nutrition research at the consumer health division of Novartis in Nyon, Switzerland, to produce an effective functional food scientists must "identify the mechanism in the body that is causing some response." That means identifying the individual proteins that carry out the process and then designing a molecule to enhance or discourage the response. Once made, such molecules could be used as food additives.

These foods won't be limited to a prescription aisle. Many common fruits or vegetables could be genetically engineered to produce vaccines for common childhood diseases. In fact, researchers at Loma Linda University School of Medicine have already genetically engineered potatoes to produce trace amounts of a cholera toxin that could immunize the diner, helping his or her system to resist cholera bacteria.

Instead of having to see a nurse to get a winter flu shot, you might be able to get immunized courtesy of your local grocery store. There, some visionaries predict, you will find prepared foods that contain a harmless component of the flu virus that activates your immune system to protect you from illness.

"More and more, the supermarket is going to become a health care provider store, rather than just a place you buy your food," de-

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MARK HAVEN

M. AARON BENJAMINSON

In a laboratory in Bay Shore, N.Y., researchers led by M. Aaron Benjaminson (*above*) are sustaining fish muscle cells and even growing modest amounts of new muscle cell components outside of a fish. The dark streak in the inset image is a tiny sample of fish muscle; it is surrounded by fibroblast cells, a major component of connective tissue. Ultimately, the work could lead to a synthetic fish fillet sandwich.

clares Theodore P. Labuza, a professor of food science and engineering at the University of Minnesota. "These products are going to be put out in the produce section," he says, adding that "there's going to be a time when consumers are confused—are they buying food or a drug?"

Although food will change, our nutritional requirements will not. Humans will always need protein, the stuff of our muscles, organs and other tissues. Chicken, beef and pork could continue to be our main sources, but many experts foresee a growing market share for others.

Protein powders, for example, are among the big sellers in the previously mentioned sports supplement category. Whey protein isolate has become popular in recent years, thanks to greatly improved methods of manufacture. Basically, whey is what remains of milk when its other main solid components, fat and casein, are coagulated into cheese curd. It was essentially a waste product of cheese making until someone noticed that it was extraordinarily high in protein and extremely low in fat and in lactose, which some people find irritating to the stomach.

Runners, weight lifters and other fitness buffs are increasingly turning to whey protein isolate because it has a very high biological value, meaning that a relatively large proportion of the protein is retained in the body for a given amount absorbed. On a scale in which egg whites are arbitrarily assigned a biological value of 100, the figure for whey protein ranges from 110 to 159—higher than any whole food and much higher than beef, which has a value of 80.

SOY: IT'S WHAT'S FOR DINNER

The advantages of powders notwithstanding, it is hard to imagine most people doing without protein with more traditional textures. Some nutritionists see fish as the protein staple of the future. But Irene Chalmers, a food writer and professor at the Culinary Institute of America in Hyde Park, N.Y., is betting on soy. "It can be made into anything: any taste, any texture—crunchy or bland or squishy or slimy. It's going to be an enormous tool," she maintains.

Those of you who have tried tofu-based mayonnaises or hot dogs are probably wrinkling your noses. But good news is on the horizon, says Dana Jacobi, author of *The Natural Kitchen: Soy!* (Prima Publishing, 1996): "The Food and Drug Administration is expected to rule by this fall that foods containing at least 6.25 grams of soy protein in a serving can be labeled as helping to reduce the risk of heart disease"—a development she believes "will give large food companies incentive to play with soy."

And when corporate America turns its attention to soy, who knows what might happen. As a sign of good things to come, Jacobi cites a new soy yogurt. In the past, the concoction earned a reputation as a gruesome substitute for the real thing, but the new product might change some minds, in Jacobi's view. "One company sent me some samples this year," she says, "and I sent them to a group of people without telling them it was soy. They called back asking where they could buy some."

As for animal protein, M. Aaron Benjaminson has a dream: producing it without the animal. Benjaminson, a researcher based in Selden, N.Y., has contracted with the National Aeronautics and Space Administration to develop systems for growing food for astronauts. While working on a system to grow edible mushrooms from human waste, "it occurred to me that not all astronauts will want to be vegetarians," he recalls (to say nothing of eating those mushrooms). A chicken coop in the cargo bay was obviously out of the question, so he came up with another idea: growing animal skeletal muscle tissue—a fillet or steak, in other words—in small chambers.

Basically, Benjaminson hopes to grow the muscle cells by stimulating them electrically, mechanically, hormonally and nutritionally. With enough tinkering, he thinks that within 10 years he will be able to grow something that has the consistency and taste of filet mignon. So far he has worked mainly with fish muscle cells and has had some limited success in producing a tiny mass of tissue that looks and smells like a fish fillet. Ultimately, he believes that such a technique could produce boneless chicken breasts for a fraction of the cost of a commercial chicken farm, without the salmonella and other harmful organisms that exist on supermarket poultry.

Clearly, in a world where a steak might come from a cow or a test tube and a head cold might be treated with a pill or a salad

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dressing, the consumer is going to need a little more help. Fortunately, grocery stores are becoming more interactive, with help not only for the confused but also for the harried.

Already, for example, cooking demonstrations show off an increasing array of ready-to-eat meals. "Supermarkets will probably become the largest employer of chefs," says Chalmers of the Culinary Institute, one of the top training grounds for chefs in the U.S. She also believes that on-line grocery stores will be a big hit—with food delivered not via shopping cart and the trunk of the car but by overnight express. In fact, an experimental refrigerator has already been built with internal bar code readers and other systems that sense what staples are running low and automatically order them over the Internet [see "Living in Technology," on page 84].

On the other hand, our ravenous, overworked descendants returning from a hard day at the office may prefer to buy premade meals at drive-in windows, as more and more of us do today. "The fastest-growing dining environment for Americans is the front seat of their car," says Met-Rx chairman Connelly.

KEEPING IT FRESH

It is unlikely that on the shelves of tomorrow's high-tech, user-friendly grocery stores the tastier, healthier wares will be offered in the same old stifling packaging and wrappings used today. Take romaine lettuce. We've all seen its mysterious transformation: from a crisp, light delight to the taste buds to a repulsive sack of foul, brown goo after a couple of weeks in a standard plastic bag. Not so in the future, Labuza says.

The trouble with storing a head of lettuce in a garden-variety plastic bag is that the lettuce is still alive, taking in oxygen from its surroundings and metabolizing it. In short order, the supply runs out. "When the oxygen level dips below a certain level, [the lettuce dies and] begins to rot," Labuza explains.

Long-term preservation depends in part on maintaining the oxygen level of the bag at an optimum level—lettuce stays crisp in an atmosphere of about 3 percent oxygen. The goal for the plastics industry is to produce a plastic bag that takes in oxygen ("respires") at precisely the same rate that the vegetable or fruit does. Polymer scientists have already made some progress in this area. River Ranch Fresh Foods in Salinas, Calif., markets to growers a line of produce bags that have variable permeabilities to carbon dioxide and oxygen. The bags can increase shelf life up to 100 percent, depending on the fruit or vegetable, according to Sannai Gong, R&D manager at River Ranch.

But ambient gases are only part of the problem. Meat doesn't last long in the presence of bacteria, and pathogens such as salmonella and some strains of *Escherichia coli* present a real hazard to consumers. One solution—irradiating food with high-energy particles—kills bacteria quickly and efficiently. Although the procedure has met with some consumer resistance, Connelly expects it to become an important technology. He envisions underground vaults filled with radioactive materials, rather like a walk-in x-ray machine: "You could drop in whole packaged food products and have them emerge stable," he asserts.

But if high-energy particles don't appeal, perhaps high pressure is more palatable. Although no one is quite sure how it works, Labuza says that pressures of 240 to 275 kilopascals (35 to 40 pounds per square inch) efficiently sterilize packaged food. "You take guacamole, put it in a plastic package and put it in a cylinder, fill it with water, and then use a piston to pressurize the whole system. In a matter of minutes, you can kill most of the spoilage and food-poisoning organisms," Labuza says.

Once sterilized, the food could be shielded from outside contamination by shrink-wrapped packaging with antibacterial molecules incorporated right into it. Thus sequestered, food should be well preserved from microbiological hazards, but it faces one other challenge: oxygen can infiltrate the packaging and cause it to become rancid. To block it, packagers have added "oxygen traps"—in some cases simply iron—that react with oxygen before it can attack the contents of the package. The payoff is packages of meat that could last several years unrefrigerated.

WILLIAM LANGRIDGE *Loma Linda University School of Medicine*

A strain of bintje potato, genetically engineered to produce trace amounts of cholera toxin, immunized mice that ate it. Clinical trials with humans are expected within a year. The edible vaccine was created at the Center for Molecular Biology and Gene Therapy at Loma Linda University School of Medicine in California.

Whatever the future may bring, it seems certain to end the refrigerator biology projects that greet most returning travelers today. Slimy vegetables, rancid meat and nutritionally bankrupt starches could also be eliminated. And test-tube chicken could be the main course.

Will our taste buds be titillated? Or will manufacturers get caught up in a frenzy and make the same mistakes soy food producers made in the 1970s, sacrificing everything—including taste—for the sake of health benefits? Let's hope they do not, or the food of the future might be old-fashioned carry-out cheeseburgers and fries.

ABOUT THE AUTHOR

JIM KLING is a science and technology writer in Bellingham, Wash. He has mixed feelings about the idea of a synthetic fish fillet sandwich.

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THE NEW METROPOLIS

Can "new urbanism" be applied to urban America? **By Jim Kling**

AHEAD OF YOU, the line of automobiles stretches off to the horizon, immobile, glinting in the early morning sun. It is rush hour, and work is 20-odd kilometers away in a gleaming tower in the center of the city. Glancing at your dashboard clock, you realize that you cannot possibly make your first meeting of the day. In front of you and to the right, meanwhile, a truck maneuvers onto the shoulder, spitefully blocking a stream of drivers trying to slip by to the nearest exit ramp. As nasty epithets and the sound of car horns fill the air, your blood pressure starts creeping upward, and you wonder for about the thousandth time if it is always going to be like this.

A vast federally funded interstate highway system, advances in automotive technologies, financial incentives to buy homes, and other factors contributed mightily to what became known as the "good life" in postwar, middle-class America. Unfortunately, as we enter the next millennium, the hidden costs of those years of plenty are becoming all too obvious, from the traffic jams that frustrate commuters to the clouds of smog that accumulate over metropolitan areas. Across the country, municipal officials are confronting the effects of an urban and suburban sprawl that not only has put more distance between workers and their workplaces but also has consumed farmlands, forests and fields and left many cities with decaying infrastructures, shrinking tax bases, and deep divisions between races and classes.

Lately some cities have rebounded, thanks to lower crime rates, tax windfalls from prospering economies and soaring tourism. Still, the underlying problems of sprawl remain, compelling planners and professors to contemplate a design for better urban living.

The good news, says Anthony Tomazinis, professor of city and regional planning at the University of Pennsylvania, is that advances in architecture and structural engineering give urban designers a lot to work with. "We are daring to ask: Can we design the ideal city?" he says. The issue is much more than an intellectual flight of fancy. In 2006, for the first time, more than 50 percent of the world's people will live in urban areas, according to the United Nations Population Division.

A high-profile civic and architectural movement in the U.S. seeks to begin redressing the problems of sprawl through a return to the smaller, centered communities of yesteryear. The movement's champions extol the virtues of mixed-use neighborhoods and closer-spaced homes, which could let residents do more bicycling and walking than riding. Expanding on the movement's basic tenets, architects such as Johannes Van Tilburg, based in Santa Monica, Calif., see buildings whose ground floors feature street-side services like restaurants, hair salons and retail stores, with offices placed above and residential units topping them all.

The movement, known as new urbanism, has its share of critics. They refer to it snidely as new suburbanism, because the handful of communities in the U.S. that were built in accordance with new urbanist principles were actually constructed far from urban centers—thus tending to contribute to sprawl rather than mitigate it. But instead of giving up on the credo, at least a few adherents are taking another look at it. In effect, they are trying to find out how cities themselves can benefit from new urbanist ideas.

URBAN TRANSFORMATION

Making new urbanist havens out of decaying, sprawling metropolises would require several remarkable developments, not least a reversal of the decades-long, postwar exodus of the middle class from the inner cities. As a first step in that direction, some city planners are revitalizing downtown areas and placing hard limits on how far out development can go. "Vacant lots will be built up, historic structures will be restored, and aging buildings will be modernized to become home to a growing urban population," says James A. Johnson, former chairman and CEO of Fannie Mae in Washington, D.C. "If it's done properly, cities will get more interesting and exciting," Van Tilburg adds.

SLIM FILMS

Mixed-use buildings constructed with advanced materials and engineering techniques could let people live, work and play in a small geographic space, drastically reducing the time and energy spent commuting.

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PHOTOGRAPHS COURTESY OF THE EVERETT COLLECTION

Like their real-life counterparts, most cinematic notions of utopian communities are based on the premise that with appropriate design people can live closer together and thus far more efficiently without missing their sprawling lawns. Many of the exterior shots in the recent motion picture *The Truman Show* were filmed in Seaside (*left*), an actual new-urbanist village on the Florida coast. In the 1936 sci-fi classic *Things to Come* (*right*), the toga-clad residents of Everytown in 2036 lived even more closely together in a brightly lit Moderne-style edifice dug into the hills. Production designer Vincent Korda supervised the creation of the sets for the remarkably prescient movie, which was based on an H. G. Wells novel.

Portland, Ore., is the shining example of a metropolis at war with sprawl. In 1979 the Oregon state legislature decreed that the metropolitan area surrounding Portland could expand only to within certain limits. By sticking to those limits, regional officials have preserved a high quality of life in the area despite a population increase from 978,000 to 1.2 million in the greater Portland metropolitan area between 1980 and 1997. "In-fill and redevelopment [of urban centers] are emphasized consciously and openly," says Robert B. Textor, emeritus professor of anthropology at Stanford University. Textor, who retired to Portland, served on a citizens' committee that drafted a statement on urban development in the city's metropolitan area that covers the next 50 years.

In some places, the division between urban development and countryside is downright stark. "You can go to Beaverton [a suburb of Portland], and there are roads with housing on the right and open fields on the left," Textor notes. "That is the urban-growth boundary. [Developers] fight it, but it's much better than places like Akron, Ohio, where you can't tell where the city ends and countryside begins, because on outlying roads you have McDonald's and auto supply stores going on and on," he adds.

But Portland's success in controlling sprawl has come at a price. As development is restricted, land and housing prices climb inevitably higher. If this upward spiral is allowed to continue, in time only the affluent will be able to afford to live in the city. Setha Low, professor of environmental psychology and anthropology at the City University of New York, argues that such an eventuality would be a major blow to the function of cities. "I think the biggest challenge facing cities right now is the integration of different kinds of people," she says. Balancing concerns about diversity with those regarding excessive growth is one of the key dualities in limiting sprawl, Low concludes.

One solution may lie in an old maxim of real estate—as the price of the land grows higher, so do the buildings. The islands of Manhattan and Hong Kong, with their signature skylines, are the most celebrated examples. It is possible, and perhaps even inevitable, that in a space of self-imposed limits the mixed-use mantra of new urbanism will be applied vertically.

In fact, at least one architect has been working on such a plan for almost three decades. Paolo Soleri initiated his Arcosanti project in 1970 near Phoenix to build and work out the details of daily life in tall buildings. In his conception, those buildings would also be mixed-use, with environmentally friendly industries occupying the ground level, topped by services and finally residential units. Some floors could be dedicated to indoor gardens, he explains, but the vertical city dweller craving the great outdoors would need only take the elevator to the ground floor, because the surrounding landscape would be preserved.

Urban-growth **boundaries** and redevelopment can **save us from sprawl,** but the price may be a **less diverse population.**

Will such a vision ever become reality? Low is pessimistic. "As long as there's open country people can move to, it will be hard to get them to change their American ideal of a little plot of land," she says.

She may be right. But to many of those motorists driving to work every day, a commute by elevator may sound like a pretty good idea after all.

ABOUT THE AUTHOR

JIM KLING is a science and technology writer in Bellingham, Wash. His daily commute is pollution-free, taking him from his kitchen through the foyer to the home office.

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THE ULTIMATE BABY BOTTLE

Are artificial wombs in our future? Was Aldous Huxley right? **By Tabitha M. Powledge**

NOBUYA UNNO brings up the nightmarish novel *Brave New World* himself, marveling at Aldous Huxley's accurate prediction that the kids are likely to be anemic after they emerge from their artificial wombs. Actually, Unno's little ones are not quite kids yet. They're fetuses. Goat fetuses.

Raising the ticklish subject of Huxley's 67-year-old novel is pretty cheeky for a scientist who has devoted a decade to developing an artificial womb. But Unno, an obstetrician-gynecologist and researcher at the University of Tokyo, might simply be acknowledging the inevitable. The novel's clever and even now slightly shocking vision of human kids fostered in jars always lurks beneath any talk of artificial wombs.

It's hard to dismiss Huxley, even though the purposes of the artificial wombs being developed at several institutions around the world differ from those described in his book. They are not the government's way of breeding a citizenry specialized for particular chores, most of them menial. Quite the opposite. They are born of consumer demand for fertility treatments and better babies.

NOT YOUR AVERAGE SIBLING RIVALRY

Today's assisted-reproduction technologies, such as in vitro fertilization, have resulted in a boom of cases of a womb with a two—or a three or a four. Indeed, it is not so rare for five, six or even more fetuses to be jammed together in a berth that was really designed for just one. One consequence has been more babies born far too early. Their tiny lungs are not ready to breathe air, so we plunk them into incubators and hook them up to respirators. The result is what doctors delicately term iatrogenic injuries, meaning damage arising from medical intervention. To wit: brain damage, blindness, intestinal damage, delays in development, mental retardation and other lifelong handicaps. So the hunt is on for safer ways to help fetuses through the transition to becoming air-breathing creatures.

Hence the artificial womb. Unno and his colleagues at the University of Tokyo call their version the Extrauterine Fetal Incubation system, or EUFI. Although incubation is its middle name, EUFI is quite different from a conventional incubator. It attempts to simulate the fetal universe.

EUFI is a double-walled, vertical acrylic box filled with artificial amniotic fluid warmed to just under 40 degrees Celsius (104 degrees Fahrenheit), the normal temperature of a nanny goat's own. The furry fetus floats in the fluid and need not breathe air. The truly critical component of the artificial womb, however, is not the container itself but its substitute for the placenta.

A biological placenta adds oxygen and removes carbon dioxide from the fetus's circulating blood, just as its lungs will do once they are fully developed. Artificial-womb scientists must mimic that ability, building a detour into the fetus's circulation so that blood passes from umbilical artery to umbilical vein, exchanging gases as it goes. The Japanese design passes the blood through a membrane oxygenator made of hollow silicone fibers; the unit looks like a thick, clear plastic tube full of straws.

Unno and his co-workers have maintained a fetal goat in EUFI for more than three weeks. (Because goat gestation is about half as long as a human pregnancy, three weeks for a goat fetus is roughly comparable to six weeks for a human one.) But none of the kids the scientists have kept in EUFI for long periods have survived

TOM WAGNER *SABA*

Goat-in-a-box? Using goat fetuses as guinea pigs, researchers at the University of Tokyo have developed the world's most advanced artificial uterus technology. They say their plastic box filled with synthetic amniotic fluid is almost ready to nurture a human fetus.

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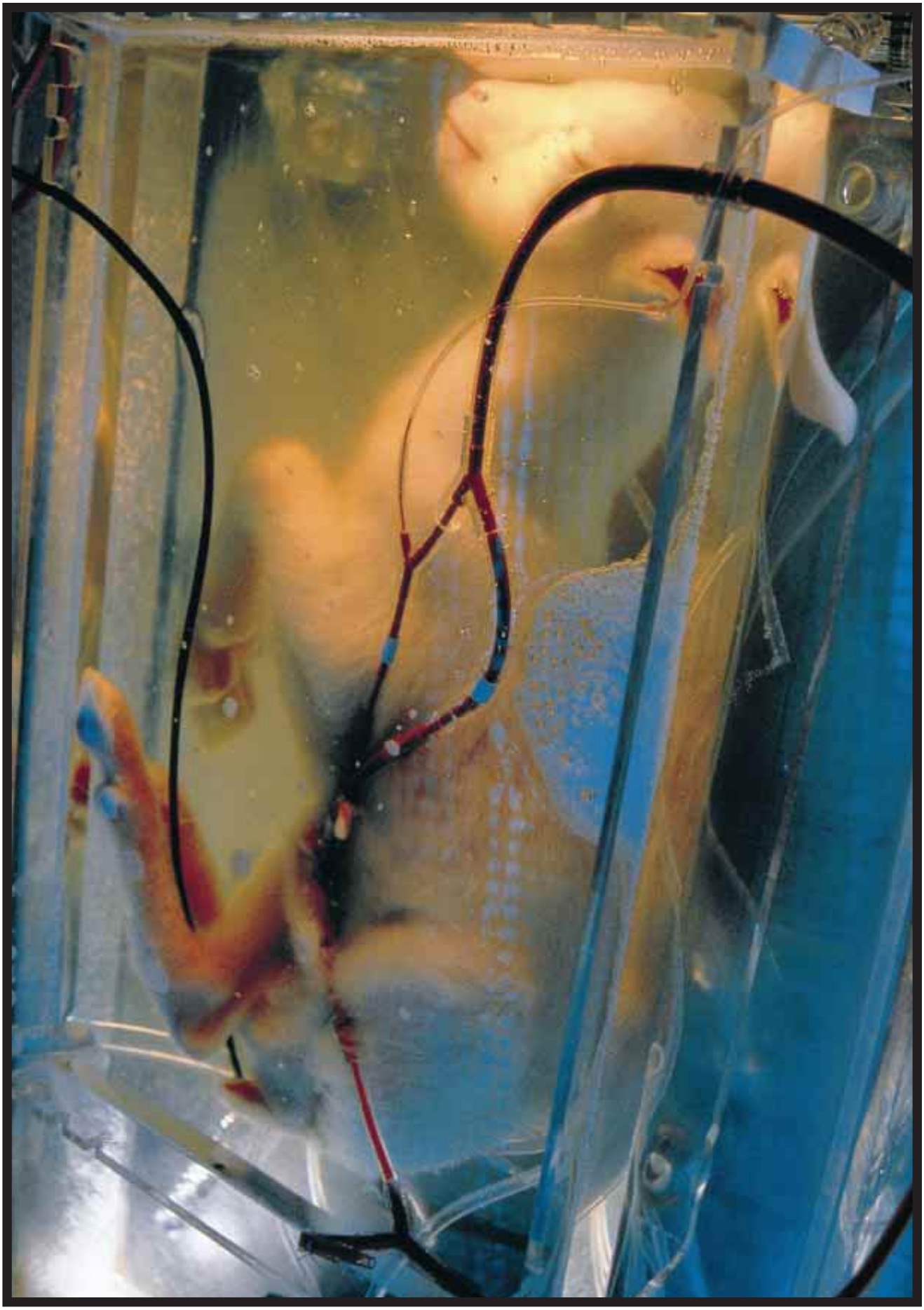

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after they were "born," even with mechanical respirators to help them breathe. The researchers have had better success removing kids from their dams for several hours or a day and then replacing them: three have been nurtured temporarily this way. Unno's theory is that his current setup doesn't allow the fetuses adequate nutrition, a problem he claims can be corrected.

"I believe, technically, we are ready to apply the concept of our system to human fetuses, although of course we need to redesign the whole system to maximize safety before actual clinical use," he says. But even at its present technical level, he suggests, the apparatus might be ready for preemies born at 25 or 26 weeks. Eventually the system could be applied as early as 23 weeks, the present record for a premature baby to be born and still survive.

The Japanese success appears to have provoked interest elsewhere. At least two other EUFI-like projects are in the works. A Spanish artificial womb, still in the design and very early testing stages, resembles Unno's. Pediatric surgeon Vicente Martinez Ibañez and his colleagues at Hospitals Vall d'Hebron in Barcelona are planning to set a sheep fetus adrift in a small transparent pool. Outside will be two fluid filters and a pump that also performs the task of an oxygenator. This pump will be connected to the umbilical blood vessels, and it will act as an artificial placenta as well.

If grant money is forthcoming, Martinez Ibañez foresees that the womb could be ready in three to five years. "Our main problem is the financial issue, but we are optimistic," he says.

HELLO, JELL-O BABY

There's also a new collaborative effort among several laboratories at Harvard University and the Massachusetts Institute of Technology to invent what researchers there call minimally invasive medical technologies. Support for the extremely premature infant is its first project, which is still very much on the drawing board. For competitive reasons, Joseph P. Vacanti, a surgeon at Harvard Medical School and a pioneer in the new field of tissue engineering, declines to discuss the group's plan for gas exchange except to say that it, too, will mimic the placenta.

"Our concept," he says, "is that we would probably have to put the baby into a semiaqueous environment in a sort of Biosphere." By "semiaqueous" he means one of the new hydrogels that can be either very liquid or fairly solid, with the degree of jelling adjusted to cushion the fetus and permit gas exchange. (But try not to think of the Boston Baby Biosphere as a bowl of Jell-O.)

To Barbara Katz Rothman, author most recently of *Genetic Maps and Human Imaginations: The Limits of Science in Understanding Who We Are,* the stated mission of EUFI and the other womb designers sounds familiar—and ominous. Every technology for newborns, from infant formula to electronic fetal monitoring, follows the same path, she asserts. "It starts off as an alternative in a tragic situation and then becomes the more sophisticated, elite way to do it."

Eventually a woman who **wants a uterus** could place her order, donate her cells and **take delivery** of her **custom-made womb** in just six weeks.

She is concerned chiefly about the consequences of raising a baby without an attachment to another human being. A pregnant woman thinks constantly about her baby; long before birth, it is part of her life. "That is very different from putting in an order and having them give you a call when it's ready."

Katz Rothman, who is also a professor of sociology at the City University of New York, recalls once asking students how

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Bioartificial bladders, such as the one now being grown at Harvard Medical School (*shown above and in incubator at left*), can serve as prototypes for a bioartificial womb. The main difference between the two organs is that wombs have thick, muscular walls for childbirth, whereas bladder walls are thinner and less structurally complex.

they would comfort a baby raised in a machine. "A guy in the back of the room said, 'Put it on top of the refrigerator!' "

She foresees—and she is not alone—that EUFI and its ilk will get better and better at helping increasingly young fetuses survive, eventually meshing seamlessly into the efforts of the assisted-reproduction technologists to get better and better at helping increasingly old embryos survive. When that happens, Huxley's imagined technology will no longer be fiction. "That will open all kinds of troubles: corporate babies and baby sales and babies being grown for God knows what purpose," she predicts.

WOMBS MADE TO MEASURE

Anthony J. Atala, a surgeon at Harvard Medical School's Children's Hospital, is taking a completely different approach to the artificial womb, one that doesn't trouble Katz Rothman at all. Atala is a tissue engineer whose idea is to grow transplantable organs from a patient's own cells. The patient's body would not reject such organs as foreign, and nobody else would have to part with a kidney or a nice piece of liver [see "Growing New Organs," on page 10].

Atala's report earlier this year about a tissue-engineered artificial bladder that works in beagles made a big splash. It took Atala and his colleagues 10 years to devise the right soup to nourish the bladder cells and to grow the bladder, which is basically a bag—a tough shape to grow in a lab.

Quick, what other well-known organ is also basically a (very muscular) bag? Guess what tissue Atala's lab is trying to engineer now? The bladder and the uterus have very different functions, of course, but Atala's plans for his womb grow out of his success with the beagle bladder. Already his lab is building the cell layers that compose uterine tissue: muscle and the spongy stuff called endometrium that lines the inside of the uterus. "We're doing very preliminary work: taking cells, placing them on a scaffold and creating small units of tissue," he explains.

Complex as it is, in a sense Atala's challenge is simpler than that of the Baby Biosphere researchers, because there's no placenta. Making its placenta is the baby's job. Atala's is just the container, one that would permit an embryo to implant and create its customary system for getting oxygen and getting rid of carbon dioxide and to provide housing until normal delivery time. "That's a long-term goal," he notes. "We are at a very elementary stage right now."

Atala wants to create a uterus that can be transplanted into women who are born without one or who have uterine abnormalities or scarring. Once the researchers know how to grow a uterus, the plan is for a woman who wants one to donate stem cells—early-stage cells that have not yet begun to specialize [see "Embryonic Stem Cells for Medicine," on page 18]. These will be grown in the lab into a uterus, which will then be surgically implanted into the woman, where it will work as if it were original equipment.

Atala predicts it might take as long as another 10 years to fashion his uterine bag because the uterus is more complex than the bladder. But eventually, he says, a woman who wants a uterus could place her order, donate her cells and take delivery of her custom-made womb in just six weeks.

"Nature does it best," Atala points out. "We can do some things in an incubator outside of the body. But during pregnancy there are so many things going on, so many hormones, such an interaction between the mother and the child. The best incubator is Mom."

Katz Rothman couldn't have put it better herself, which is why Atala's bag doesn't worry her one bit. "A uterus inside a woman's body, that's fine. To me that is not an artificial womb," she declares, suggesting instead that it's more like contact lenses or a prosthetic arm. "You're extending the body and making the body work. That is very different from pregnancy without a body."

Still, there's one possible use for Atala's bag that, while it might not bother Katz Rothman, would certainly discombobulate a lot of other people. To say nothing of transfiguring human culture, politics and the psychology of sex, reversing hundreds of millions of years of evolution, and giving birth to a new division of the fashion industry:

Welcome to the 21st century, when men can get pregnant.

ABOUT THE AUTHOR

TABITHA M. POWLEDGE is a freelance science writer who lives near Washington, D.C. She is the author of *Your Brain: How You Got It and How It Works* (Scribner, 1994). She does not want an artificial uterus.

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FUTURE SCHLOCK

By Steve Mirsky

WELCOME TO the last page, unless you mistook this magazine for a Passover Haggadah, in which case, welcome to the first page. Either way, we may ask: How is this issue of this magazine different from all other issues? Here's how. Most issues detail the knowledge that has already been discovered, the research conducted yesterday; this issue predicts tomorrow. And prediction is fraught with peril, especially when it's about the future.

Mark Bradley knows the dangers of prophecy better than most. The *Atlanta Constitution* columnist wrote the following after his town's Braves roughed up the New York Yankees in the first two games of the 1996 World Series: "It's doubtful the Yankees can take so much as one game.... We are no longer watching a competition. We are witnessing a coronation." Prince Charles may get a coronation before the Braves, who lost the next four.

Scientists tend to be relatively intelligent, which may explain why one of them, physicist Werner Heisenberg, came up with his famous uncertainty principle. Most nonscientists assume that science provides ironclad certainty. Working scientists avoid certainty like a *Yersinia pestis* infection, because certainty is the mother of embarrassment. For example, if that once unforeseen invention the World Wide Web is to be believed, ancient Roman engineer Sextus Julius Frontinus said, "Inventions have long since reached their limit, and I see no hope for further development." Only he probably said it in Latin. In 1895 topflight scientist Lord Kelvin ignored the lessons of the birds and the bees when he allegedly insisted that "heavier-than-air flying machines are impossible." Two wrongs don't make a right, but two Wrights made an airplane. It was in all the papers.

Prediction is fraught with peril, **especially** when it's about **the future.**

Speaking of the papers, in 1921 the *New York Times* dismissed Robert Goddard's early thrusts at rocket science. "Goddard ... does not know the relation of action to reaction and of the need to have something better than a vacuum against which to react." Nature abhors those who misunderstand vacuums, and 48 years later the *Times* recanted with the headline "MEN WALK ON MOON."

Poor Thomas J. Watson, former CEO of IBM, is haunted so frequently by his bad prediction that I almost feel guilty for bringing it up yet again. Almost. "I think there is a world market for maybe five computers," he supposedly said. Tom, I have four computers in my house. (And those are only the ones I'm aware of. For all I know, my toaster has a computer in it.) But I'll cut Watson some slack. In 1943, when he revealed his market analysis, computers were unwieldy behemoths. They were still distressingly huge in 1949 when *Popular Mechanics* made the accurate but limited prediction that "computers in the future may weigh no more than 1.5 tons." One of my four weighs three pounds. And it can run a disk that contains the entire *Encyclopedia Britannica,* which ordinarily weighs another 1.5 tons. Ken Olson, founder of Digital Equipment Corporation, climbed out on Watson's limb when he reputedly said, "There is no reason anyone would want a computer in their home." How could he have known that without computers in homes the endless e-mail stream of bad jokes, chain letters and Neiman-Marcus cookie recipes would be available only at work.

Browsing through old issues of *Scientific American* reveals that this publication has occasionally had problems with the reception on its crystal ball. In 1846 we preferred the paddle wheel to the screw propellers that currently power most motorized vessels bobbing on bodies of water. "It is truly astonishing," we wrote, "that men of capital in England persist in keeping themselves so totally ignorant of the plain philosophical principles of Mechanics, as to suppose that a propeller of any form on the screw principle, can compete with the simple Fultonian paddle-wheel." Besides being notoriously slow, however, paddle ships have another problem: as a ship rolls, more of one side of the paddle is submerged. That side provides more power. This unequal distribution makes for some dicey steering, which is at least partly behind today's paucity of paddle-driven aircraft carriers churning through the North Atlantic, despite our unique grasp of the "principles of Mechanics."

Of course, it is easy to make sport of the brave few who were willing to subject their beliefs to public scrutiny and came up short. Those who make predictions that hit the mark tend to be more easily forgotten. So let it be for the intrepid souls who have put their assertions on the line in these pages. May their prognostications be so accurate that we forget they ever made them. And should you, dear reader, be tempted to attempt prophecy, remember the immortal words of Damon Runyon: "The battle is not always to the strong, nor the race to the swift. But that's the way to bet."

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ABOUT THE AUTHOR

STEVE MIRSKY is a contributing editor at *Scientific American*. He predicted that the Super Bowl would be won by a football team, the Masters by a golfer and the Kentucky Derby by a nose.

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